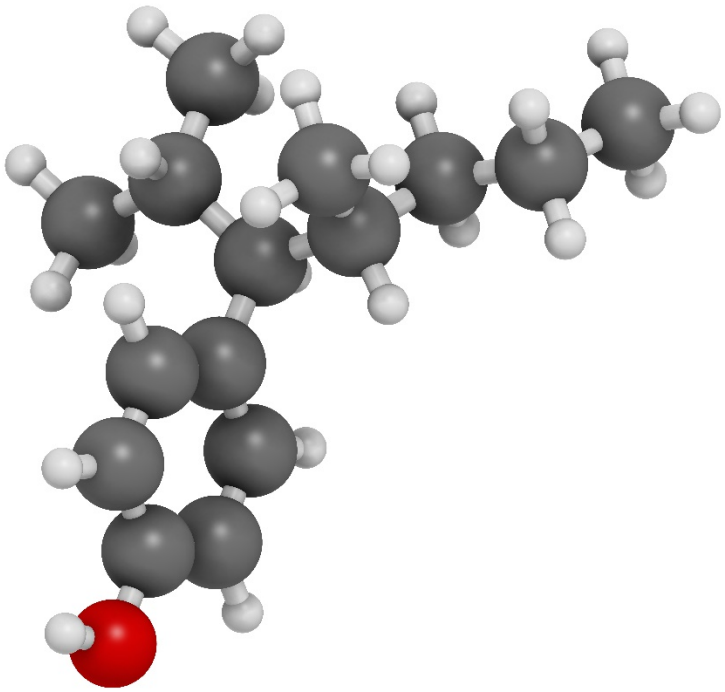
STUDY

Requested by the PETI committee

European Parliament

Endocrine Disruptors: from Scientific Evidence to Human Health Protection

PETITIONS



Policy Department for Citizens' Rights and Constitutional Affairs
Directorate General for Internal Policies of the Union
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EN

Endocrine Disruptors: from Scientific Evidence to Human Health Protection

STUDY

Abstract

This study, commissioned by the PETI Committee of the European Parliament, presents the scientific knowledge regarding the health effects of endocrine disruptors, a class of hazards recognized in EU regulation since 1999. This report reviews the scientific evidence regarding the concept of endocrine disruption, the extent of exposure, associated health effects and costs. The existing relevant EU regulations are discussed and recommendations made to better protect human health.

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DISCLAIMER

To repair is twenty times more difficult than to prevent.

Henri-Frédéric Amiel (1821-1881)

Truth is ever to be found in the simplicity, and not in the multiplicity and confusion of things.

Isaac Newton (1643-1727)

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit and Hyperactivity Disorder
BBP	Benzyl butyl phthalate
BPR	Biocidal Products Regulation (2012)
CLP regulation	Regulation on Classification, Labelling and Packaging (2008)
DBP	Dibutyl phthalate
DES	Diethystilbestrol (drug)
DDE	Dichlorodiphenyltricholoenthylene (metabolite of DDT)
DDT	Dichlorodiphenyltrichloroethene (insecticide)
DEHP	Bis(2-Ethylhexyl) phthalate
DIBP	Diisobutyl phthalate
EAP	Environment Action Program
ED	Endocrine Disruptor
EFSA	European Food Safety Authority
FDA	Food and Drugs Administration (USA)
GHS	Globally Harmonised System
IQ	Intellectual Quotient
OECD	Organisation for Economic Co-operation and Development
PBDE	Polybrominated Diphenyl Ethers
PCB	Polychlorinated biphenyls
PPPR	Plant Protection Products Regulation (2009)
RIVM	Dutch Institute for Public Health and the Environment
SCCS	Scientific Committtee on Consumer Safety (European Commission)
WHO	World Health Organization
WoE	Weight of Evidence

LIST OF TABLES

LIST OF FIGURES

EXECUTIVE SUMMARY

Background

The endocrine system orchestrates our physiological functions from conception onwards. Endocrine disruptors (EDs) were recognised by the scientific community in 1991. In 2002, the World Health Organization defined EDs as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations." Thousands of scientific publications have identified several modalities of ED action, chronic diseases linked to ED exposure and provided a first estimate of population impact in the EU. The EU identified this issue as early as 1996 and has since recognized EDs as a new type of health and environmental hazard, together with carcinogens, mutagens, substances toxic for reproduction (CMRs), persistent, bioaccumulative and toxic (PBTs) substances. With REACH (2006) and the Plant Protection Products (2009) regulation, specific sectors of the regulation began considering EDs.

Aim

This report presents the scientific evidence regarding the concept of endocrine disruption, the extent of exposure and of the health effects of EDs. The relevant EU regulations are reviewed and recommendations made to change them for better protection of human health.

Main conclusions

Scientific knowledge on EDs

Hormones coordinate harmonious development and function of all organs and act at minute concentrations (part per trillion to per billion range). Given the essential role of the endocrine system during development, ED exposure during vulnerable periods can induce long-lasting changes, with adverse effects in the short and long terms; some of these effects are expected at very low-doses. Non-monotonic dose responses can be observed. Hundreds of man-made and some natural chemicals can disrupt the function of the endocrine system. Certain of them have been demonstrated to induce adverse effects as a consequence of this disruption.

Although multifactorial, many chronic health disorders have been clearly linked by experiments on cells and animals and epidemiology to EDs. These disorders include obesity and metabolic disorders, male and female reproductive disorders, reproductive cancers, thyroid disorders, neurodevelopmental disease and IQ loss.

EDs are present in food, food contact materials, cosmetics, consumer goods (including furnishings, cleaning products), toys, as well as drinking water. Consequently, the EU population is widely exposed to known and suspected EDs. This fact is confirmed by biomonitoring studies, including on susceptible subgroups such as pregnant women and children. Annual costs related to ED exposure were estimated to be €163 billion (above €22 billion with a 95% probability and above €196 billion with a 25% probability).

Multiple exposures result in cumulative effects, a situation expected for compounds acting via similar pathways, and that is also likely for compounds acting on similar health outcomes via different pathways. Synergistic effects can also be observed. Currently, EU chemical regulations do not generally consider these cumulative effects, notably for ED exposures.

Scientific consensus now exists for (1) the definition of endocrine disruptors; (2) the presence of suspected or recognized EDs in the environment and in humans in the EU; (3) EDs as a serious concern

for the health of current and future generations and the environment; (4) the limitations of current regulatory approaches used to identify so-called safe thresholds and (5) the lack of consideration of cumulative effects of combined exposures in regulations.

Regulation of EDs in the EU

Minimising overall exposure of humans and the environment to EDs is a relevant aim for the EU, as expressed in the 7th Environmental Action Program and 2018 EU framework on EDs.

Attaining this goal requires a) a cross-sectorial ("horizontal") definition of EDs, distinguishing three categories according to the level of evidence; b) a guidance document explaining how to apply the definition using test results and scientific literature to identify EDs; c) tests covering all ED modalities; d) legal requirements to make these tests compulsory in application dossiers; e) a management logic, which could distinguish sectors with likely human exposure (where EDs should be avoided) from those for which exposure is rare.

Currently, a legal definition of EDs only exists for biocides and plant protection products (pesticides), the sectors with the most advanced EDs regulation in the EU. The Guidance document for biocides and plant protection products is thorough and, if correctly used, can help identifying EDs. However, even for pesticides, the regulation is imperfect, in that a definition and a management logic exist (zero exposure to EDs in pesticides) but without ED tests covering all ED endpoints being compulsory in application dossiers, making ED identification very difficult in practice.

This lack of efficient consideration of EDs is more pronounced in other sectors where human ED exposure is also very likely, such as food additives and food contact materials (including non-plastic food contact material), cosmetics, toys, consumer goods and workers' protection.

Test development: there is an urgency to accelerate test development and validation, especially in modalities beyond steroid hormones. Coverage is currently insufficient for the thyroid axis, metabolic hormones and the corresponding endpoints. Regulators should rely more on academic publications when assessing ED properties and request faster test validation.

Test requirements: the regulatory documents setting out the content of application dossiers for authorization generally do not require tests that would allow to scientifically assess if the substance under evaluation is an ED. Regulations setting test requirements in all sectors with possible ED use should be modified to include provisions ensuring that dossiers contain test results allowing to conclude if the evaluated substance or product is an ED.

Management of EDs across sectors: In order to minimize ED exposure among EU citizens, the EU should move towards identical management of EDs across all sectors for which ED use is very likely to entail population exposure, notably pesticides, food contact materials and additives, consumer goods, cosmetics, medical devices and toys.

Specifically, given the widespread EU population exposure to many suspected EDs and the fact that combined exposure to several EDs acting on similar or different pathways can have cumulative effects, to minimize ED exposure and render EU regulation more coherent across sectors, a logic similar to that already in use for pesticides (no human exposure) appears justified in sectors with likely human exposure.

The oestrogenic, androgenic, thyroid, steroid loads, and that of other ED modalities, in consumer products, food, cosmetics and drinking water should be evaluated and monitored, and the implementation of limit values in such media considered.

Research needs

Besides test development, six research areas should be prioritised: (i) Epigenetic effects of EDs; (ii) Effects across generations; (iii) ED effects on the microbiome, (iv) Green (safe) chemistry; (v) Novel ED modalities and (vi) Characterization of dose-response functions for ED effects in humans.

Table 1: Overview of the existing EU framework regarding protection from the health effects of endocrine disruptors.

	Regulatory steps to protect health				
Sector	**Definition of EDs**	**Guidance document**	**Tests**	**Test requirements**	**Risk management logic**
Plant protection products	Y	Y	I	I	Y
Biocides	Y	Y		I	Y
REACH chemicals	I	N		I	I
Cosmetics	N	N		N	N
Food additives	N	N		N	N
Food contact material	N	N		N	N
Drinking water	N	N		N	N
Toys	N	N		N	N
Workers' regulations	N	N		N	N
Medical devices regulation	Y	N		I	Y

I: Insufficient/needs reinforcement. N: None or very limited. Y: Yes, satisfying existing regulation.

PART A: SCIENTIFIC KNOWLEDGE ON THE EFFECTS OF EDs

1 CONCEPTS OF ENDOCRINE DISRUPTION

KEY FINDINGS

- The endocrine system controls our main physiological functions from conception onwards.
- Hormones are present in body fluids and act at very low concentrations (usually in the part per trillion to part per billion range).
- Certain man-made and natural chemicals can disrupt the function of the endocrine system and consequently induce adverse effects. These substances are referred to as endocrine disruptors (EDs).
- EDs act at low doses, with different effects during vulnerable exposure windows. Non-monotonic dose responses can be observed.
- Given the essential role of the endocrine system during human development, ED exposure in vulnerable periods can induce organizational changes, with adverse effects occurring in the short and long terms, such as congenital malformations, altered neurodevelopment and IQ loss, metabolic disorders (type-2 diabetes, obesity) and specific "endocrine-related" cancers such as breast and prostate cancers. In adulthood, ED exposure has been associated with reduced fecundity and thyroid disorders.
- Multiple exposures can result in cumulative effects, a situation that is expected for compounds acting via similar pathways, and also probably for those acting on similar health outcomes via different pathways. Synergistic effects can also be observed.

This report deals with the health impact of endocrine disruptors (EDs) and the corresponding regulatory framework in the European Union (EU).

A number of thorough scientific reviews and reports on endocrine disruption have been published since 2010, underlining the importance, the concern and the rapid growth of the field. At the end of 2011, the EU commissioned a "State of the Art Assessment of Endocrine Disrupters" [1]. In 2012 the World Health Organization (WHO), with the United Nations Environment Programme (UNEP), published their "State of the Science of Endocrine Disrupting Chemicals" [2]. That year WHO also published "Endocrine Disrupters and Child Health", underlining the overriding importance of protecting vulnerable groups such as pregnant women, children and adolescents [3]. In 2015, the Endocrine Society produced their second report on the question, with over 1300 references to different aspects of endocrine disruption [4]. Then, in 2016 UNEP commissioned the International Panel on Chemical Pollution (IPCP) to do three reports on EDs, each published in 2018 [5-7].

Here, our aim is not to systematically review the literature in these reports, but to provide an overview of health impacts, current regulatory framework and suggestions for changes. The report is structured in three parts; **part A** presents the scientific knowledge regarding the concept of endocrine disruption (chapter 1) and the extent of the impact of EDs in the EU (chapter 2). **Part B** addresses the current EU regulatory framework, while **part C** suggests improvement for this framework distinguishing the

identification of EDs (chapter 4) and the risk management logic (chapter 5). Though EDs also impact our environment, on which our health depends, here, the discussion is limited to human health concerns.

1.1 A short history of the discovery of endocrine disruption

1.1.1 The insecticide DDT

In 1962, Rachel Carson's book *Silent Spring* [8] galvanised public attention on effects of excessive use of the insecticide DDT on wildlife. The population losses in fish and birds observed then were not simply due to reductions in a main food source, insects, but also to accumulation of DDT (and its metabolites) in their organs. Astutely, Carson realised that this in turn was affecting their reproductive capacity. For the emblematic "bald eagle" (the USA's national symbol), the massive decrease in population was in large part due to increased fragility of the egg shell that broke under the parents' weight. Although Carson never employed the term *endocrine disruption*, she was in fact describing this phenomenon, as DDT has since been shown to reducing circulating levels of the sex hormone, oestradiol in birds [9, 10] and to alter prostaglandin (a family of chemical messengers related to the hormonal system) levels, thereby interfering with enzymes needed for shell mineralization. She also presciently realized that humans would be contaminated through their food, and that effects would later be seen on human health. This is unfortunately the case. Half a century later, it was reported that girls (female foetuses) who had been exposed to high levels of DDT *in utero* during the 1960s have an increased risk of breast cancer in the following 50 years [11].

1.1.2 The drug diethylstilboestrol (DES)

DES was developed as a synthetic oestrogen. It was prescribed from the 1940s onwards. Prescriptions were based on the erroneous assumption that it could prevent miscarriage and other pregnancy complications, which was shown to be wrong in 1953 [12]. In 1971, the USA Food and Drug Administration (FDA) advised against its use due to vaginal cancers occurrence in girls born to mothers who had used DES, while this cancer usually develops post-menopause. DES was banned in the Netherlands in 1975 and in France and Spain in 1977. Women who took DES have a slightly higher risk of breast cancer [13], but the most striking effects are seen on offspring exposed during pregnancy [13]. Epidemiology shows *in utero* DES exposure to be linked not only to vaginal cancer in daughters of exposed women, but also to reproductive tract disorders, infertility and higher rates of spontaneous abortion [13]. Sons display higher rates of genital abnormalities, and increased risks of prostate cancer; in addition, an increased risk of testicular cancer has been suggested [14]. Importantly, effects such as increased risk of malformations of the male genitalia and possibly attention deficit and hyperactivity disorders (ADHD) are also observed in the grandchildren of DES-prescribed women [15, 16].

In contrast to DDT, which is persistent in the body, DES is quickly eliminated, showing that chemicals can exert effects long after they disappeared from the organism, possibly on successive generations. There are biological mechanisms whereby the organism could keep a memory of exposure. One possibility relates to adverse effects that can be traced to epigenetic modifications. Work on animal models shows that certain DES impacts could result from epigenetic effects on the germ cells (the sperm and egg cells) forming in the *in utero* DES exposed foetuses (see 1.7 and [17]).

Both DDT and DES provide examples of compounds able to interact with the endocrine system in humans or wildlife species (DES was designed to mimic a natural hormone, oestrogen; DDT and its metabolites were found to alter hormone production, mimic oestrogen and block androgen actions) and to cause adverse effects. They resonate with a concept developed in 1.7 and 1.9: the Developmental origin of Health and Disease (DOHaD)[18], underlining foetal life as a determinant factor for child and adult health.

1.1.3 Endocrine disruption is defined in 1991

The Wingspread conference (1991) defined and detailed the global problem of endocrine disruption in both wildlife and humans, emphasising that developmental exposure could lead to disease later in life [19]. At the time, focus was on reproductive problems, so the principal concern was interference of chemicals with the two main classes of receptors that control reproduction — the receptors for oestrogens and androgens, two classes of steroid hormones[1]. In 1996, the EU piloted, with the OECD and other organisations, a meeting of scientists and regulators at Weybridge in the UK[2]. The Weybridge meeting presciently noted the need for research on effects of EDs on health and wildlife beyond those principally studied, the reproductive steroids.

1.2 Definition of endocrine disruptors

The definition of EDs proposed by the World Health Organization (WHO) and International Programme on Chemical Safety (IPCS) in 2002 [9] is now widely accepted scientifically:

> "An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub)populations." [9]

An *adverse effect* is defined as:

> "a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences." [3]

Definitions of substances with endocrine-disrupting activities are now present in the EU regulation in the context of plant protection products and biocides (see 3.2 and 4.2 below).

1.3 Relevant knowledge from endocrinology

1.3.1 Endocrinology is the study of hormones and their controls

Hormones are produced in endocrine glands, for example the ovaries, testes, thyroid, and pancreas, amongst others (See Annex 1). Hormones are released into the blood stream. By acting on multiple distant organs, the endocrine system ensures harmonious coordination of tissue function. Before the foetal endocrine system is functional, maternal hormones ensure foetal development.

The endocrine system regulates all physiological systems: growth of the skeleton and muscles, reproduction including puberty, digestion and metabolism, control of body temperature, brain development and brain activity including mood and alertness. Hormones produced by the pancreas control sugar levels, other hormones (glucocorticoids) govern stress responses. Hormones affect immune responses, hence responses to vaccination and disease. The endocrine system has a continual dialogue with the two other main communication systems of our body, the nervous system and the immune system, so that any disruption of the endocrine system may also impact these other systems.

[1] Steroids are organic molecules with four benzenic rings with (among others) a signaling role in the body. Steroid hormones include the androgen class (those controlling the development of male reproductive function, with testosterone as the main androgen hormone) and oestrogen class (with *oestradiol* as the major oestrogen hormone in humans).
[2] http://www.iehconsulting.co.uk/IEH_Consulting/IEHCPubs/EndocrineDisrupters/WEYBRIDGE.pdf
[3] REGULATION (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. Link.

1.3.2 Hormone act at very low doses within three main endocrine axes

The main endocrine axes are the hypothalamo/pituitary/gonad axis controling reproduction and puberty, the hypothalamo/pituitary/adrenal axis that controls many aspects of our stress responses and the hypothalamo/pituitary/thyroid axis, that controls thyroid hormone, needed for brain development and function, growth and control of energy metabolism.

Hormones are secreted into the blood and act on target tissues throughout the body at extremely low concentrations (typically in the part per trillion to part per billion (ppb) range [4]). These effects are explained by the high affinity of receptors and other proteins (transporters, metabolic enzymes) for their endogenous hormones.

The endocrine system also includes the proteins in the blood system that distribute the hormones, the enzymes involved in hormone synthesis, activation and inactivation, the membrane transporters allowing hormone entry into target cells and the hormone receptors themselves (found on the cell membrane, in the cytoplasm or in the nucleus).

Not surprisingly, disruption of the endocrine system can affect negatively each of these levels. Certain EDs interfere with hormone synthesis and distribution or transport, others with hormone-receptor interactions. The overall result can be adverse effects on development and growth, brain function and behaviour, metabolism and energy balance.

Interference with the reproductive system can alter timing of puberty and increase the risk of certain cancers (e.g. breast, prostate and testicular cancers). EDs that affect thyroid hormone production, distribution or action, which can affect brain development and function. Hence, thyroid disruption has been implicated in the increased incidence of neurodevelopmental disease; other disease links are suspected in relation to thyroid disruption, including certain forms of thyroid cancer [20-22].

Hormones act through nuclear receptors. Nuclear receptors behave as transcription factors that directly control gene expression. In humans there are 48 nuclear receptors, including those that bind the sex hormones (oestrogens and androgens) and thyroid hormone. ED research has largely focused on these, but we know that many other receptors are also ED targets, including many nuclear receptors implicated in metabolism, such as the peroxisome proliferator activated receptors (PPARs) [23, 24].

EDs that interfere with any level of hormone production, entry into cells, metabolism and action, will affect the level of the endogenous hormone in the target cell. As such, EDs can directly modify gene transcription responses within target cells, even though they may act upstream (i.e. by interfering with distribution of hormone).

1.3.3 Non-linear responses are seen for endogenous responses and in endocrine disruption

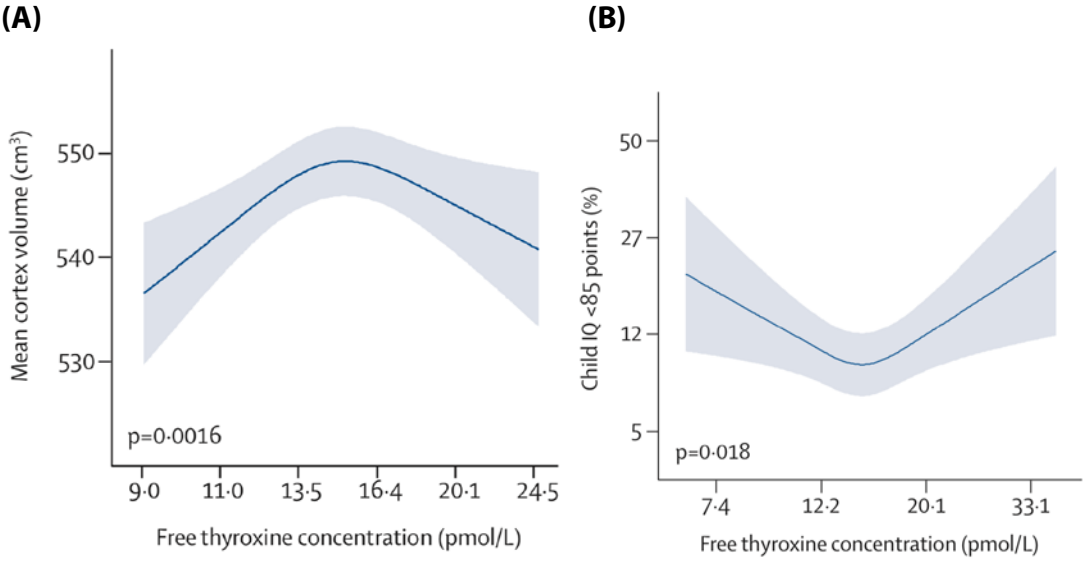
A key characteristic of both endogenous hormone responses and particularly in the case of ED action is their non-linearity and that they display non-monotonic dose response curves [25] (see Figure 1). Both changes above or below the optimal hormonal level can be detrimental, as seen in the case of thyroid hormone levels during pregnancy (see Figure 1). When it comes to the effect of EDs, this implies that stronger physiological effects can sometimes be seen at lower ED doses than at higher doses. This concept is contrary to many toxicological scenarios where effects increase as the dose increases. Thus, the principle that "the dose makes the poison" (understood as "the effect of the poison increases with the

[4] One part per billion corresponds to the dilution of a drop of water in an Olympic swimming pool. One part per trillion is a thousandth of a drop diluted in the same volume.

dose") is not generally valid for EDs[5]. For some EDs, low exposure levels can have stronger effects than higher exposures. Hence, trying to characterize dose-response functions and identify safe thresholds by testing a small number of doses (usually three in some regulatory tests) may be inefficient for EDs.

There are a number of physiological explanations to this phenomenon. In the case of endogenous hormones, non-monotonic responses are often due to desensitisation and internalisation of receptors or negative feedback effects. In the case of EDs, other factors also enter into play. One type of explanation relates to differences in tissue sensitivity and response to a given ED, so that different tissues are affected at different doses [26]. An example is the sensitivity of the rat hypothalamus to gestational bisphenol A exposure, where effects can be seen at 2.5 µg/kg [27], which is lower than the current EFSA tolerable daily intake (TDI) for humans (4 µg/kg). Second, different receptors can be implicated in the same tissue and activated at different doses. An example is the pancreas, where differential dose-responses are observed to bisphenol A, according to the receptor activated [28].

Figure 1: Relation between maternal thyroid hormone level (thyroxine) during pregnancy and (A) offspring cortex volume at the age of 8 years; (B) the predicted probability of offspring having an Intellectual Quotient (IQ) at the age of 6-8 years below 85 points. As women with overt hyperthyroidism or hypothyroidism were excluded, the range of values corresponds to those that can be considered within the normal limits for pregnancy, i.e. 7 to 34 picomole/l of free thyroxine [29].



1.3.4 The endocrine system plays essential roles from conception to aging

Endocrine signalling is implicated in the fine control of every stage of development from the earliest stages of organogenesis (organ formation), growth of all foetal structures through to timing of birth, placental function, all aspects of early post-natal life and childhood, puberty and adolescence. It is also implicated in reproduction (including control of egg and sperm production), other key functions in adulthood (metabolism, temperature control, brain function) and ageing [30]. In consequence, perturbation of the endocrine system can influence susceptibility to a large range of disease and disorders, from congenital malformations, growth and metabolic disorders (overweight, type-2 diabetes),

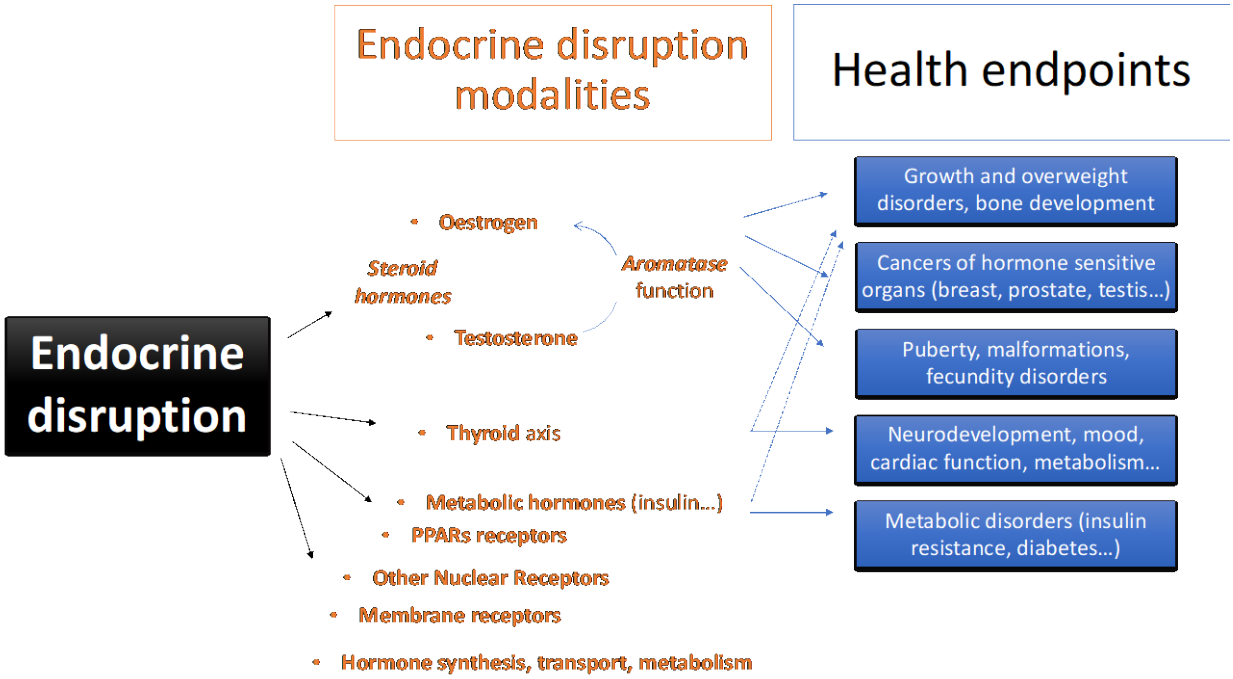
[5] Note that this is also true for environmental exposures other than EDs. For example, the relation of temperature with mortality follows a U-shape pattern, with high mortality both for the lowest and highest temperatures.

fecundity, neurological disorders, cardiovascular disease and cancers in hormonally-sensitive tissues such as the breast, prostate, testis... Some EDs likely to elicit such effects are listed in 1.8.

1.4 Fine scale evidence that exogenous substances can interfere with the endocrine system

Multiple sets of data demonstrate that EDs interfere with endogenous endocrine signalling at the molecular and cellular levels. In many cases, this allows one to deduce the molecular target and hence the ED mechanism of action. However, one must note that there are several adverse effects observed in animal studies and at the level of populations (see 1.5 and 1.6) without the corresponding mechanism(s) of action to be yet known. Here, four examples are chosen underlining the fact that in certain cases the molecular events are known (see also Figure 2).

Figure 2: Schematic overview of the main modalities and health endpoints that can be affected by endocrine disruptors.



1.4.1 Interference with the oestrogen or androgen binding to their receptors

Many EDs have the capacity to interfere with oestrogen binding to the oestrogen receptor (ER), providing the basis for screening tools based on interactions of EDs with the two main types of oestrogen receptors [31]. Similar cell-based or *in vitro* tools have been developed for the androgen receptor (AR) [32]. Additional screening tests have been developed for many other nuclear receptors, in human cells and cells from model organisms [33]. However, the thyroid hormone receptor cannot readily be used for such cell-based screening methods, as the ligand binding domain of the thyroid hormone receptor is highly specific and as many other levels of thyroid disruption have been identified as more likely modes of action for thyroid axis disruptors [34].

1.4.2 EDs affecting aromatase action

Many EDs have been identified as interfering with the enzyme aromatase, which converts androgen to 17 oestradiol (an oestrogen) by demethylation. Aromatase is a cytochrome P450 enzyme, essential for an astonishingly wide range of physiological functions, with roles in the placenta, ovarian follicle development, bone mineralisation, glucose homeostasis and brain function [35]. One of the most striking roles of aromatase includes post-natal masculinisation of different areas of the brain [36]. In humans, aromatase is strongly expressed in brain areas associated with control of reproduction and behaviour [37]. Not surprisingly, EDs modulating aromatase expression have been associated with multiple reproductive [38], as well as neurodevelopmental and behavioural disorders [39]. As for the oestrogen and androgen disruptors, cell-based screening methods have been developed to detect aromatase disruption [40].

To date, there is a long list of EDs demonstrated to modulate aromatase activity at the level of gene expression, including bisphenol A, polychlorinated biphenyls (PCBs), certain phthalates and various pesticides [4].

1.4.3 ED Interference with thyroid hormone distribution in the blood

Hormones act as messengers at distance from their site of production and are carried to their target cells in the bloodstream on distributor proteins. Three main distributor proteins convey thyroid hormone and are targets for multiple EDs [41]. The physiological consequences of displacement of thyroid hormone from its distributor proteins will ultimately be a decrease in circulating thyroid hormone levels due to changes thyroid hormone metabolism by the liver. Such changes could be particularly adverse during early pregnancy, when the foetal brain is entirely dependent on maternal thyroid hormone supply. EDs that are known to alter the equilibrium between distributor proteins and thyroid hormone include certain pesticides, flame-retardants and perfluorinated compounds.

1.4.4 Interference with iodine uptake by the thyroid gland.

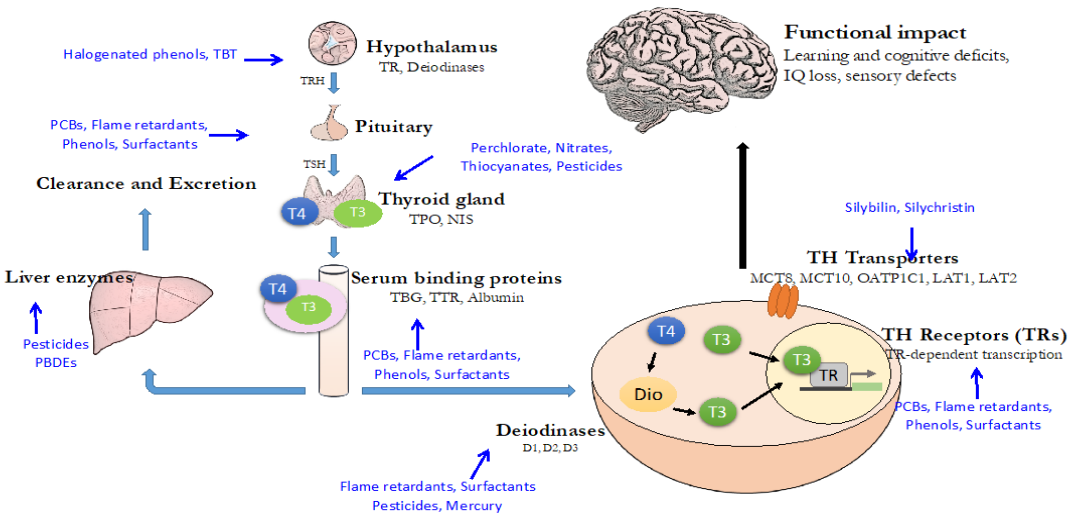
Iodine is needed for thyroid hormone production by the thyroid gland. Both iodine deficiency and thyroid hormone deficiency are known to adversely affect brain development, cause IQ loss and increase the risk of neuro-developmental disease [34]. A number of EDs impede iodine uptake by the thyroid gland, including perchlorate, nitrate and thiocyanate. Perchlorate exposure is widespread and can modulate maternal thyroid hormone during pregnancy [42]. Perchlorate contamination has been reported in amniotic fluid [43]. Mild iodine deficiency is present and is even increasing in various parts of Europe [44]. Iodine deficiency (due to perchlorate, thiocyanate or nitrate exposure or insufficient dietary sources of iodine) could therefore exacerbate the effects of ED exposure, especially during pregnancy.

Beyond these examples related to the oestrogen, androgen and thyroid modalities, interactions of xenobiotics with other key nuclear receptor such as PPARs (implied in lipid metabolism, and for which disruption can entail impacts on metabolic disorders such as overweight or type-2 diabetes) have been identified [45].

1.5 Evidence available at the scale of organisms and populations

Going now from the molecular and cellular levels to the organism, there is no shortage of animal studies and human epidemiology demonstrating that EDs interfere with multiple physiological systems, even at low doses. Here we have chosen recent examples on EDs and the links with male and female reproduction, brain development and brain function, metabolic diseases such as obesity.

Figure 3: Known and suspected EDs linked to adverse effects on neurodevelopment. Note that the multiple levels by which EDs can interfere with thyroid hormone signalling complicates the setting up of *in vitro* screening methods for each level of action. This is particularly acute given the multiplicity of thyroid hormone actions during brain development [46, 47]. Different structures (cell, brain) are not drawn to scale. Adapted from [33].



NIS: Sodium Iodide Symporter; PCB: Polychlorinated biphenyl; T3: tri-iodothyronine (most active form of thyroid hormone); T4: thyroxine (less active form of thyroid hormone); TH: Thyroid Hormone; TBT: Tributyl tin; TPO: Thyroid peroxidase; TR: Thyroid hormone Receptor.

1.5.1 Compounds affecting brain development through alteration of the endocrine system

Both epidemiological and experimental studies have shown that prenatal exposure to multiple EDs can diminish IQ or increase risk of neurodevelopmental diseases. Many of the EDs act through altering thyroid signalling (for recent reviews see: [34, 48]), but other players, including EDs affecting androgen and oestrogen signalling can be implicated in neurodevelopmental disorders, especially in the context of sexual differentiation of the hypothalamus [49].

Some of the best studied EDs adversely affecting neurodevelopment include PCBs. Their production was banned in the 1970s, but PCBs are still present in human fluids today due to their persistence. Reductions in cognitive function and up to 5 IQ points loss have been observed for highest maternal PCBs exposures [50, 51]. There is a long list of other known or suspected EDs that can affect brain development, including both phosphorylated and brominated flame retardants, some phenols, phthalates, perchlorate and mercury (Figure 2). Mercury is also an ED in that it interferes with the deiodinases that activate and inactivate thyroid hormone. All deiodinase enzymes contain selenium which is chelated by mercury [52].

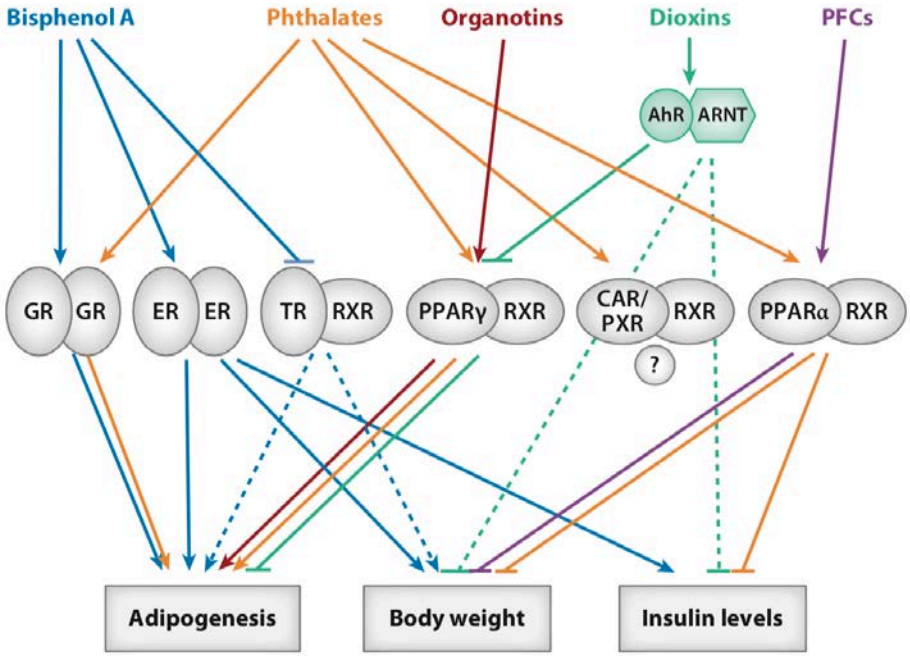
1.5.2 Compounds altering diabetes risk and other metabolic disorders through alteration of the endocrine system

Overweight and obesity development is a huge health concern in the EU, including but not only because of its influence on type-2 diabetes and life expectancy. Recognized risk factors of these multifactorial conditions include limited physical activity, high energy intake and poor diet. In addition, it has been demonstrated that environmental chemicals in generals, and some EDs in particular, can contribute to the development of overweight and obesity (Figure 4). A clear example of such an *environmental obesogen* is that of bisphenol A. A working group from the French environmental health agency (ANSES) reviewed the scientific literature and concluded that "bisphenol A may increase metabolic disturbances eventually leading to type-2 diabetes." [53]. The mode of action has been shown to be endocrine

disruption and the effects were judged relevant for humans because of the similarity between the considered animal models and humans in terms of insulin production, and because of in vitro evidence based on human cells [53]. Another systematic review of the animal literature further indicated that effects were observed below exposures of 50 µg/kg body weight/day [54], while the current tolerable daily intake of 4 µg/kg body weight/day for bisphenol A in the EU assumes a lack of adverse effect below 400 µg/kg body weight/day[6].

Additional examples of EDs implicated in obesity development include the case of tributyl tin (TBT, a banned compound used as in anti-fouling paints), with studies on mice showing both effects on the first generation and transgenerational effects [55]. Studies on other models have implicated triclosan and benzo(a)pyrene in metabolic disruption [56].

Figure 4: Overview of the relations of suspected EDs with nuclear receptors implicated in the development of adipogenesis and metabolic disorders such as insulin resistance. From [45].



AhR: Aryl hydrocarbon Receptor. ER: Oestrogen receptor. GR: Glucocorticoid receptor. PPAR : Peroxisome Proliferator Activated Receptor . PXR: Pregnane-X Receptor. RXR: Retinoid X Receptor. TR: Thyroid hormone Receptor.

1.5.3 Compounds inducing reproductive disorders through alteration of the endocrine system

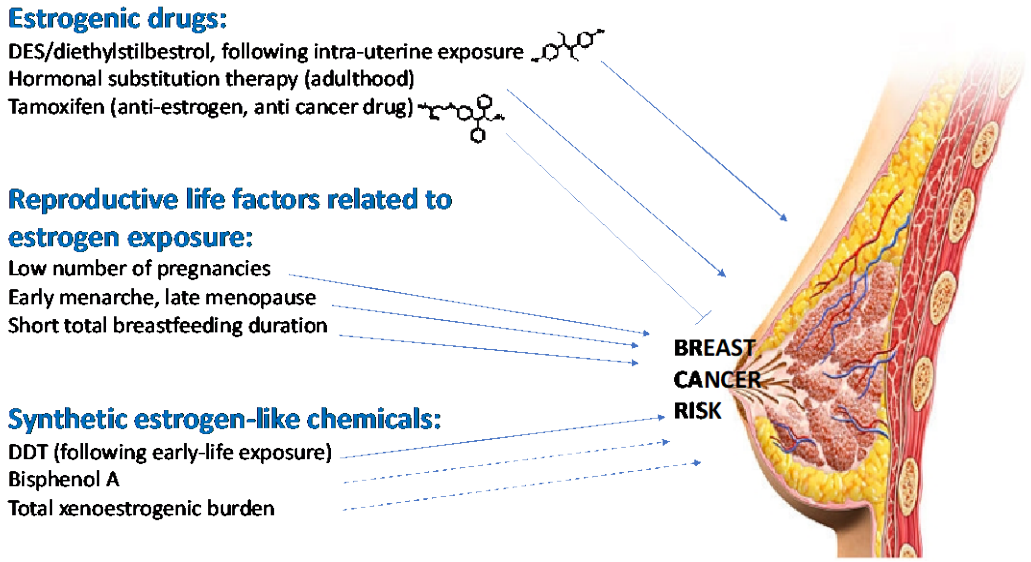
Besides reproductive cancers (*e.g.* of the testis, prostate or breast), many confirmed and suspected EDs have been implicated in multiple reproductive disorders in men and women, from reduced fertility and fecundity (longer time to pregnancy), but also to modified ovarian cyclicity [57], endometriosis and fibroids[7] [58]. Epidemiology and animal experiments have often focused on male reproduction, testicular dysgenesis and decreased fertility [59, 60], with costs for male health effects estimated at around 15 billion euros per annum in Europe [61]. Those EDs most clearly linked to male reproductive disorders include specific phthalates (such as DEHP), which, in the case of prenatal exposures, have been linked to

[6] Given that a safety factor of 100 is generally used to derive an authorized level from the lowest dose at which tests can detect an effect.
[7] Fibroids are tumours of the uterus that are non-cancerous in their vast majority.

cryptorchidism, hypospadias, reduced anogenital distance [62, 63]. Epidemiological data has linked endometriosis incidence to phthalates [58] and animal models endometriosis to benzophenones, dioxins and phthalates [64, 65].

Experimental work has shown maternal exposure to EDs (DES, vinclozolin, bisphenol A and PCBs) to adversely affect hypothalamic controls on reproduction and to exert multigenerational effects through epigenetic mechanisms, including altered DNA methylation patterns [66]. Similarly, work on animal models has shown ED exposure to affect mating behaviour [67, 68].

Figure 5: Examples of compounds with oestrogenic or anti-oestrogenic activity that may influence breast cancer risk.



1.5.4 Implication of oestrogen-like compounds in breast cancer

Strong evidence has accumulated since the 1970s for an implication of oestrogens in the incidence of breast cancer. First, reproductive life factors associated with an increased risk of breast cancer include a small number of pregnancies or children, a short total duration of breastfeeding, an early menarche and late menopause, all of which tending to indicate a role of exposure to natural hormones secreted during the menstrual cycles as increasing breast cancer risk [69]. Second, drugs such as diethylstilboestrol (DES), a synthetic oestrogen, has been shown to increase breast cancer risk following intra-uterine exposure (see 1.1.2). Third, the first efficient drug against breast cancer is Tamoxifen, a potent anti-oestrogen [70]. Fourth, regarding industrial chemicals, intrauterine exposure to the insecticide DDT has been identified as a probable risk factor of breast cancer incidence in a prospective cohort study with a 50 year follow-up [71]. Bisphenol A, which interacts among others with the oestrogen receptors, is also a possible risk factor for breast cancer, promoting mammary cell growth [72]. Fifth, epidemiological case-control studies conducted in Spain documented the xeno-oestrogenic burden (corresponding to the overall oestrogen-like activity from molecules stemming from outside the body) as being a predictor of breast cancer incidence [73, 74]. This evidence of the implication of the oestrogen-like activity in breast cancer is synthesized in Figure 4.

1.5.5 Implication of other potential EDs in cancer risk

Several potential EDs have been identified as influencing other types of cancer; this is in particular the case of chlordecone, a chlorinated (now banned) pesticide that increases prostate cancer risk [75];

bisphenol A, for which experimental evidence shows effect on prostate cancer [72]; DES and clear cell adenocarcinoma of the vagina [76]. Increased incidence of papillary thyroid cancer has also been linked by epidemiology or experimental work to EDs, including flame-retardants and biocides [20-22].

1.6 EDs can act additively and synergistically

1.6.1 Different types of effects of mixtures

In an industrial, commercial or toxicological context, mixtures are sometimes restricted to intentional mixtures, such as the list of active substances, adjuvants, stabilizers and excipients composing marketed products like biocides, drugs or cosmetics. However, from a public health perspective, it is also relevant to consider mixtures of other origins, such as discharge mixtures (e.g., the list of effluents of an industrial site), coincidental and environmental mixtures (combination of substances in one environmental compartment from different sources, e.g. the presence of metals, persistent pollutants, pesticides and chemical additives in the diet) and, more generally, the situation of combined exposure. This expression of *combined exposure* refers to exposure to multiple chemicals by multiple routes, from one or multiple sources and/or use(s) [77].

In addition, (i) as there are mechanisms whereby the body may keep a memory of an exposure even if the compound is not persistent and has been excreted (e.g. through epigenetic mechanisms), (ii) since the effect of an environmental factor on health can be delayed, and (iii) given that many chronic diseases, such as cancers, are assumed to occur as a result of a multi-hit multi-step process, the question of the effect of combined exposure is also a concern for *protractive exposures*, i.e. exposures that have occurred at different times rather than simultaneously. We will use here the term *mixture* in this broadest meaning of combined exposure to chemicals that may or may not have the same source, route of exposure, mode of action, type of effect and may even not be present in a given organism at the same time.

The question of the possible effects of the biological and health effects of several chemicals jointly present in the organism is a classical topic for pharmacology as some patients need to take several drugs [78]. Given the widespread exposure to many environmental contaminants, many of which with potential health effects in the general population (see section 2.7), whether mixtures of chemicals affect health is no longer a question limited to patients, but is of importance for all population groups from foetuses to the elderly.

Generally, several situations can occur when the organism is exposed to a mixture:

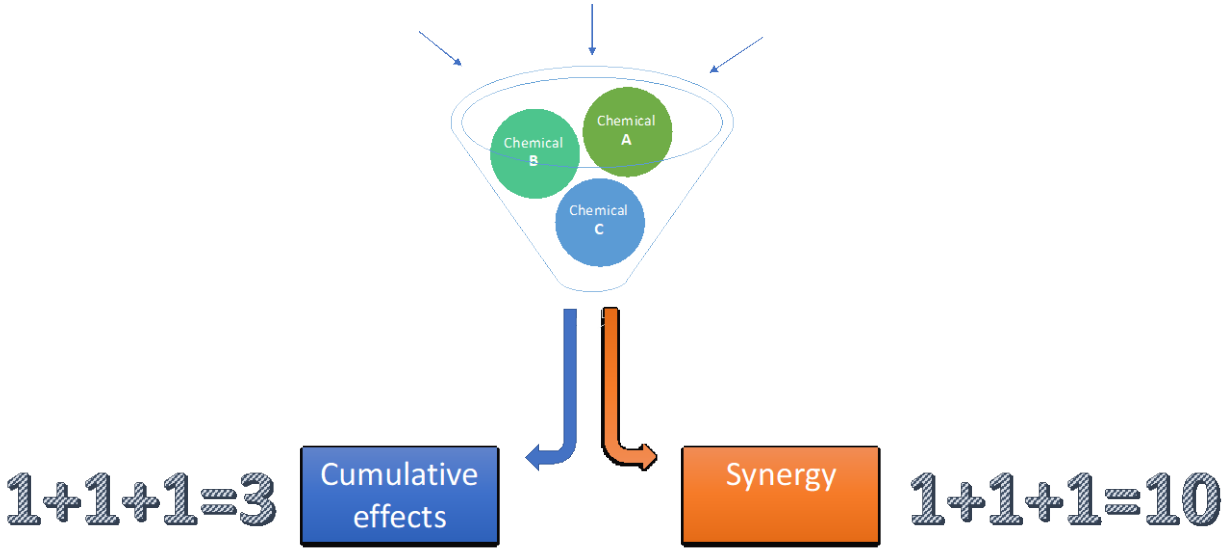
a) Each chemical is present at a dose that would not have a detectable effect in the case of an exposure to the chemical alone, and the mixture has no detectable effect either (*lack of observable effect*);

b) Each chemical is present at a dose that may or not have an observable effect in the case of an exposure to the chemical alone, and the mixture has an effect that can be predicted from the dose-response function of each of the chemicals. Typically, the effect of the mixture might be equivalent to the sum of the responses induced by each of the chemical alone at the dose at which it is present in the mixture (response addition, see 1.6.2 below), or to the effect of one of the chemicals at a dose corresponding to the sum (or a weighted sum) of the doses of all the chemicals (dose addition, or *cumulative effect,* see 1.6.3 below);

c) Each chemical is present at a dose that may or not have an observable effect in the case of an exposure to the chemical alone, and the mixture has an effect that *cannot* be predicted from the dose-response function of each of the chemicals; for example, the effect of the mixture might be stronger (*synergy*) or weaker (*antagonism*) than the sum of the effects of each chemical.

The expression "cocktail effect" is sometimes used to refer to situation c) or jointly to situations b) and c). Situations b) and c) are depicted in Figure 6. Both situations b) and c) are, generally, ignored by regulatory (with exceptions, see below) and common practice outside the situation of drug prescription to patients.

Figure 6: Different types of health effects of mixtures of hazardous chemicals. Note that in addition to synergy, antagonism is also possible (omitted for simplicity).



1.6.2 Response addition ("independent action")

Historically, regulatory toxicology (i.e., the regulatory approach to toxicology) has considered (i) that most compounds act according to a threshold, i.e. that there is a safe threshold below which a given hazardous compound does not elicit a biological response (see 2.9); this assumption is generally still applied in regulatory toxicology for most hazardous compounds with the exception of carcinogenic and genotoxic compounds; and (ii) that the response of a mixture of chemicals can, when the compounds act according to different modes or mechanisms of action[8], be predicted by combining (usually summing) the responses of the population to each of the chemical at the considered exposure level. For example, if animals are exposed to 15 chemicals, each at a dose able to induce a given same effect in the exposed group for single-compound exposure, then the response addition model would predict that the effect is equivalent to that of one of the chemicals present at 15 times this dose. If each of the 15 chemicals is present below the estimated safe threshold, then the model predicts that the mixture will not induce an adverse effect.

This situation of response addition is also referred to as "independent action", because it is the response classically assumed for compounds that have independent modes of action, i.e., through different biological pathways (i.e., one through an oestrogenic action and another one through an anti-androgenic mechanism).

Response addition is the general approach that will lead to the lowest safe levels because this model assumes that one can be exposed to a large number of compounds, each being below its "safe level",

[8] Mode of action and mechanism of action are defined in appendix I page 83.

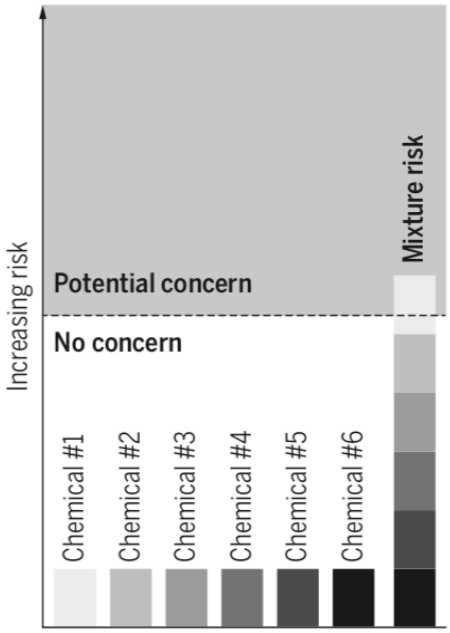
without any adverse effect to occur (this is assuming that none of the compounds act via the same pathway, which is actually generally done by the current regulatory approach to combined exposure).

1.6.3 Dose addition (cumulative effects)

Another situation in which the effect of a mixture can be predicted from the independent effect of each of its components is that of dose addition (or equivalently *concentration addition*). Cumulative effects correspond to a situation in which the mixture effect corresponds to the effect expected from a single chemical present in the mixture but at a dose corresponding to a weighted sum of the doses of all the mixture components. The concentrations of each compound are weighted according to a factor decreasing with the dose required to reach a certain effect (e.g., occurrence of the adverse effect considered in 10% or 30% of the population). We will call this situation of dose addition a situation of cumulative effects, to be distinguished from response addition described in 1.6.2.

For example, exposure to 6 compounds with identical dose-response slopes each present at 20% of the dose expected to cause a given health effect (e.g., disease occurrence in 30% of the population) when present alone may produce the same effect as the single exposure to one of these chemicals at 6x20%=120% of the dose expected to cause this effect, as illustrated Figure 7. In this situation, the response addition model would, in contrast, predict a lack of adverse effect.

Figure 7: Illustration of the cumulative effect of a mixture of compounds each present in the body below a dose that would be a concern in the case of a single exposure, but for which the mixture constitutes a risk. From [79].



1.6.4 Synergy, antagonism

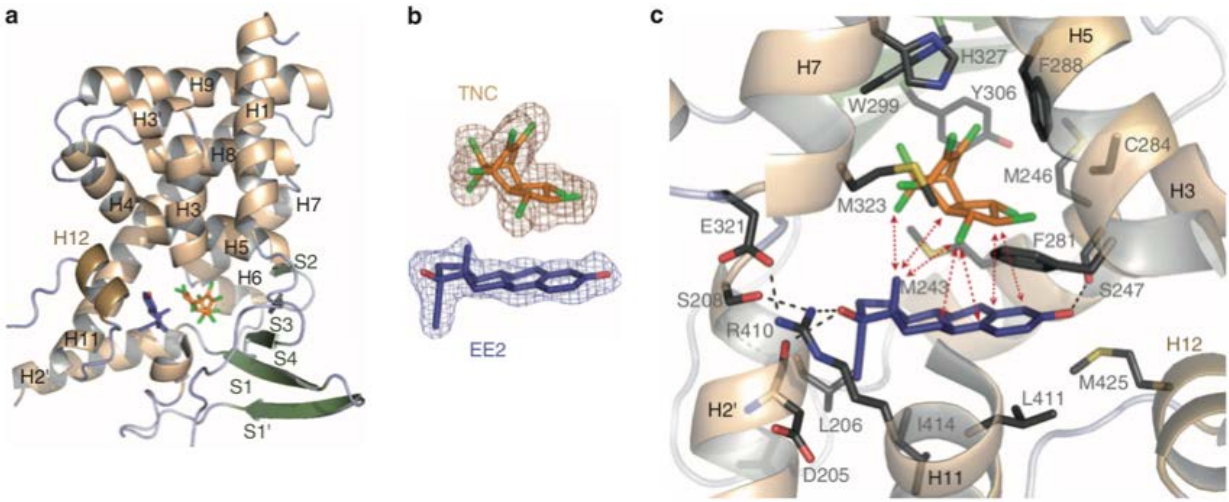
Synergism is used to refer to the situation when the effect of two or more compounds on a specific endpoint (e.g. the occurrence of a clinical effect) is stronger than that predicted by "adding" the concentrations or the effects of each of the compounds considered alone. Well-known examples of synergy include the effect of catalysts in chemistry (allowing a reaction to take place while no reaction

would occur without the catalyst) or, in pharmacology, those between alcohol (ethanol) and specific drugs, whose effect is potentiated by ethanol, or between grapefruit juice and several drugs.

Synergism or antagonism may occur because of metabolic effects of either compound in the mixture, or any effect on a system that will modify the availability of the other compounds. For example, synergy of xenobiotics with grapefruit juice is explained by grapefruit juice disrupting the action of enzymes of the cytochrome P450 family, a group of enzymes implicated in the metabolism of many drugs and xenobiotics in general [80]. Regarding endocrine disruptors specifically, bisphenol A has been shown to alter the gut permeability [81], which can be expected to modify the effect of other hazardous substances present in diet.

Another explanation of synergy at the molecular level and specific to EDs has recently been characterized [82]. Forty chemicals were tested alone or in binary mixture for agonistic effects on pregnane-X-receptor (PXR), a nuclear receptor regulating the body's defence against xenobiotics. The authors observed additive effects for most pairs of compounds, suggesting that the effect of most binary mixtures of these chemicals on PXR could be predicted through a dose-additive (cumulative) effect. However, one pair of compounds, trans-nonachlor (an organochlorine pesticide) and 17 -ethinyl-oestradiol (the active component of the contraceptive pill), showed supra-additive effects. A similar supra-additive (synergistic) effect was observed for other combinations of steroid and organochlorine compounds. Molecular studies allowed to understand the mechanism of this supra-additive effect, in that the two chemicals could *simultaneously* bind to PXR, with 10- to 30-fold increased avidity compared to each compound alone. They further showed that trans-nonachlor and 17 -ethinyl-oestradiol built a supramolecular compound interacting with PXR (Figure 8).

Figure 8: Synergy between EDs - Example of a supra-molecular ligand composed of *trans*-nonachlor and 17 -ethinyl-oestradiol. a) Pregnane-X receptor (PXR) in which trans-nonachlor (TNC) and 17 -EE (EE2) are bound. b) TNC and EE2 molecules. c) Visualization of the interactions between the molecules TNC and EE2, creating a supra-molecular ligand in the ligand-binding pocket of PXR [82].



Another clear example of synergy between EDs is that of an experiment in which rats were simultaneously exposed to a phthalate (DEHP), to two fungicides present in food and to finasteride, a pharmaceutical; these four compounds are known to exert anti-androgenic effects, but according to different mechanisms [83]. For some of the endpoints considered, such as changes in anogenital distance (AGD) and sex organ weight, the effect of the mixture could be predicted by dose addition. However,

regarding the most adverse endpoint, namely malformations of external sex organ, the effect of the mixture was synergistic.

1.6.5 Which of the different mixtures models is expected to be most valid?

Historically, regulatory toxicology assumes that the situation of dose addition will occur in the case of a mixture of different compounds acting on a given biological pathway [77]; it is not expected to occur in the case of synergy or antagonism (see 1.6.4), nor, again according to the original concepts of regulatory toxicology, in the case of a mixture of compounds assumed to act according to different pathways.

However, over the last twenty years, a large number of studies have challenged this assumption. In academic toxicology, the view is increasingly that, for compounds acting on similar diseases, the mixture effect can generally be predicted using a dose addition model, even if it is not certain that they share the same mode of action. In a review on mixtures published in 2007, Kortenkamp [84] mentioned that "…combinations of EDs with similar effects are able to act together at doses that when used alone do not lead to observable effects. The experimental evidence is in line with the assumptions of dose addition."

Since then, the evidence supporting the fact that response addition should not be seen as the default model has continued to increase. We describe here a few examples.

Gaudriault et al, tested the effect of mixtures of anti-androgenic chemicals on testosterone production in an organotypic model of human foetal testis explants [85]. They reported that the effect of chemicals selected for their effects on testosterone production was higher in the case of a simultaneous exposure to several of these compounds than when each compound was alone; the effect of the mixture was generally compatible with a cumulative effect corresponding to dose addition (Figure 9A). As an example, the bisphenol A dose causing a 50% reduction in testosterone production was divided by approximately 4 in the presence of 3 other chemicals impacting testosterone, and by approximately 10 in the presence of 7 other chemicals addition (Figure 9B). Furthermore, several of the chemicals, when combined, where able to act at levels that would not have produced observable effects had they been alone.

For phthalate exposure, it was concluded that concentration addition is the relevant approach to use for the assessment of risk due to multiple sources [86].

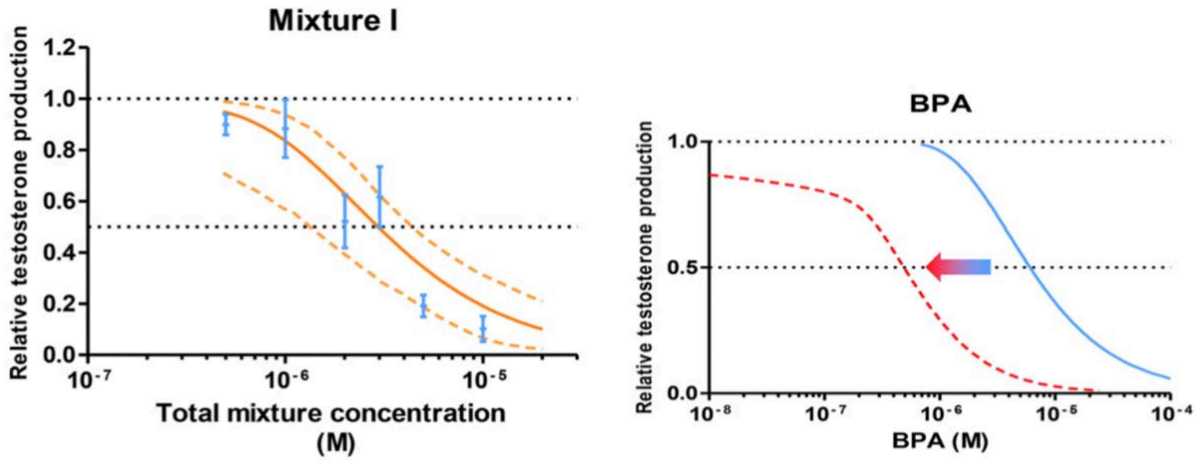
To cite another example, Lukowicz et al. [87] fed rats a combination of common pesticides at non-toxic doses that independently were without adverse effect. Their results showed that exposure increased the incidence of metabolic disease. The obesogenic and diabetogenic effects of the pesticide mix were gender-specific, in that females were most significantly affected.

1.6.6 How to handle cumulative effects and synergy in a regulatory context

The question of handling of combined exposures is of huge practical importance for regulation. Indeed, many hazardous chemicals are regulated under the logic of authorized level, that is estimated from experiments in which a single exposure is present, and assuming that the compound, if present below that authorized level, will not pose a strong risk, even if other compounds are simultaneously present. This is in particular the case for many EDs in the context of REACH chemicals (bisphenol A is for example regulated with a tolerable daily intake currently set at 4 µg/kg body weight per day), cosmetics, food contact materials (see chapter 3).

Figure 9: A) Observed effect of a mixture of anti-androgenic compounds on testosterone production in fetal testis explants (blue vertical lines) and effect predicted on the basis of dose-addition (orange continuous curve). B) Effect of bisphenol A on testosterone production when

used alone (blue curve) or in presence of a mixture with 7 other compounds (red dotted curve) [85].



Contrarily to the situation of cumulative effect, which is expected to be very general, it is too early to state at which frequency synergy between compounds might occur. In other words, it is currently unclear which proportion of EDs can show synergy or antagonism with another chemical.

Currently, the regulatory framework of EDs little considers cumulative effects. In a few cases, when a limit concentration is set for a compound in products, the limit applies to the sum of the concentrations of a small group of compounds (for example, in plasticised toys and childcare articles, a limit of 0.1% in weight is set for the sum of three phthalates: DEHP, DBP, BBP). However, this approach remains very rare, and is far from considering all chemicals acting on the same endpoint, nor even according to the same mechanism.

Generally, there are several options to manage the risk incurred by cumulative effects and synergy in regulation [79]. These include:

a) Lowering the existing authorized levels estimated ignoring mixtures by dividing them by a factor that takes into account exposure to other compounds that may act in a cumulative manner with the chemical considered; for example, if there are 10 chemicals that have the same authorized level and that are expected to act cumulatively on a given health endpoint, all authorized levels could be divided by 10. Such an logic has been formulated as the Mixture Assessment Factor, or MAF, put forward by RIVM [88].

b) Banning hazardous chemicals for which cumulative effects can be expected (i.e., get rid of hazardous mixtures in order to get rid of mixture effects);

1.7 Some populations are more vulnerable to EDs

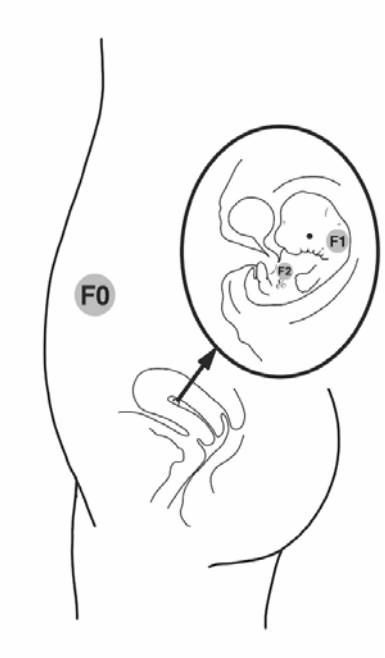
As mentioned in 1.7, pregnancy and early postnatal life (infants and toddlers) are exceedingly sensitive periods for ED exposure [89]. This is not surprising, given the fact that it is during these periods (especially early pregnancy) that all the organs (brain, liver, muscles, skeleton) are formed and that certain endocrine feedback mechanisms are not yet mature [90]. It also explains why pregnant women are advised to avoid medication, other than that prescribed.

Several lines of evidence show that many childhood and adult diseases, including cardiovascular disease, obesity and metabolic disorders including type-2 diabetes, certain reproductive cancers, neurodevelopmental disease and IQ loss, are consequences of ED exposure during pregnancy [90]. Even

though there is less data on childhood and adolescence, given their marked dependence on the endocrine system, adverse ED effects are suspected, and have been documented on animal models [91] and in epidemiological studies [92, 93].

What is more, during pregnancy, not only are the mother and the foetus exposed, but also the next generation via the germinal cells (the eggs and the sperm) that are forming in the unborn child (Figure 10). During foetal development, significant changes in methylation patterns in the germ cells occur, with complex waves of DNA demethylation and re-methylation occurring modulating gene expression through epigenetic changes. These may contribute to the extreme sensitivity of the developing foetus.

Figure 10: Exposure in pregnancy touches three generations: mother (F0), foetus (F1) and the next generation through the germinal cells growing in the foetus (F2).



1.8 Diseases and adverse effects suspected to be linked with ED exposure

Table 2 provides an overview of some of the recognized or suspected effects of EDs on human health, together with an indication of the level of evidence.

Of course, pointing out diseases whose occurrence can be influenced by ED exposure is not enough to provide an estimate of the *disease burden* (or population impact) occurring because of ED exposure at the population level. This is because in the context of multifactorial diseases, translating the *health effects* (the hazards) of a substance into a *population impact* (the risk) requires knowledge on the frequency (or distribution) of exposure in the population considered and on the dose-response function relating exposure with disease occurrence.

Table 2: Some recognized or suspected adverse effects of potential EDs.

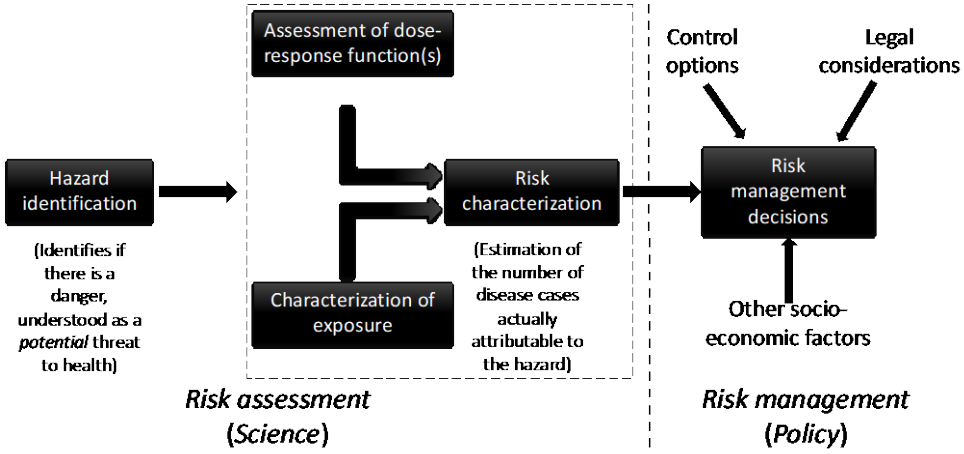
	Adverse effects				
Compounds	**Metabolic disorders**	**Neurodevelopment, thyroid function**	**Reproduction**	**Cardiovascular effects**	**Cancer and other**
Pesticides					
DDT*		Thyroid homeostasis (*VL*)	Menstrual function (*P*), early foetal loss (*S*)		Breast cancer (*P*) Environmental impacts
Organophosphate pesticides		Neurodevelopmental changes, cortex thickness, Lower IQ (*VL*)			
Triclosan	Increased BMI (*S*) and head circumference (*P*)	Neurobehavioral changes (*P*)			(Environmental impacts)
Drugs					
Paracetamol			Cryptorchidism, altered testicular function (*VL*)		
DES* (pregnancy)			Uterine malformation (*C*), hypospadias (*P*)		Vaginal cancer (*C*), breast cancer (*VL*)
Other chemicals					
Bisphenol A	Growth and overweight (*VL*)	Anxiety and hyperactivity disorders (*VL*). Memory performances (*P*)	Reproductive process (*P*)	Effects on cardiac function (*P*)	Breast and prostate cancer susceptibility (*P/VL*)
Benzophenones					
DEHP (phthalate)		Modified thyroid function, Lower IQ (*VL*)	Cryptorchidism and testicular function (*VL*)		
Flame-retardants					
Brominated flame retardants (PBDEs)		Lower IQ (*VL*) Increased ADHD risk (*VL*)			
Phosphorylated flame retardants		Thyroid homeostasis (*C*)	Reduced male fertility (*S*)		
Perfluoroalkyl substances	Growth (*S*)	Thyroid homeostasis, for PFOA and PFOS (*VL/C*)			Testis and kidney cancers, for PFOA (*S*)
Mercury		Neurodevelopmental toxicity, lower IQ (*C*)			
PCBs*		Modified thyroid function (*C*), Lower IQ (*VL*)	Reduced fertility (*P*)		
PBDEs		Modified thyroid function, Lower IQ (*VL*)			

* Banned compound (at least for use during pregnancy for DES).
The letter indicates the level of evidence: C: Certain or almost certain; VL: Very likely; P: Probable; S: Suspected.
PBDE: Polybrominated flame retardants.

Indeed, ideally, a transparent and relevant decision-making process in environmental health issues requires an estimation of the overall impact of each option on human health and the environment (the overall "risk" in the risk management terminology), and possibly of the associated costs. This overall risk can be obtained by identifying the hazards potentially associated with each option (e.g., the use of a given chemical substance), that is the health effects that may occur in certain subgroups of the population, under some exposure circumstances; by characterizing the dose-response function corresponding to each of these hazards induced by the substance, and by assessing the distribution of exposure in the population. By combining these parameters, and repeating the assessment for all possible hazards related to a substance and all substances of a given group (e.g., endocrine disruptors), one can obtain an estimate of the overall health impact of the group of substances (Figure 11). This approach has so far been applied to EDs as a whole in one study (see 2.8). As a crucial step, it requires a good characterization of the hazards associated with exposure to each ED, which we review here briefly.

These results (Table 2) illustrate the variety of adverse health effects that can be induced by exposure to specific EDs, from metabolic disorders (overweight, type-2 diabetes), to adverse reproductive outcomes, altered thyroid function, neurodevelopmental disease and certain cancers such as breast or prostate cancer.

Figure 11: Schematic view of the steps between the identification of the hazard related to a substance and its management by authorities. Adapted from [94].



1.9 Epigenetic effects and potential effects on successive generations

As explained in 1.7, the contact of a pregnant women with EDs exposes three generations (see Figure 10). Such *multi-generational effects* have been demonstrated for the grandchildren of women prescribed DES during early pregnancy, including congenital malformations [16] and possibly neurodevelopmental disorders such as Attention Deficit/Hyperactivity Disorder (ADHD) [15]. Reproductive disorders have been recorded in both sons and daughters, with the latter being most affected, notably by vaginal cancer and difficulties to conceive [95].

Transgenerational effects in this context refer to effects that are observed beyond the grandchildren (or F2 generation), i.e. in the generation(s), not directly exposed *in utero* (F3 or beyond, see Figure 10). To date, only animal studies on models with short generation times (mainly rodents) have provided such demonstrations. Transgenerational effects have been shown for a number of EDs. Examples include transient DDT exposure of F0 rats and increased obesity in the F3 generation [96], as well as impaired glucose tolerance, a factor linked to type-2 diabetes [97]. Similarly, for tributyl tin (TBT), exposure of pregnant mice to this ED predisposes unexposed F4 males to obesity [55]. In this case, differential DNA methylation (an epigenetic modification) was shown in sperm and adipose tissue of mice that were the third and fourth generation descendants of the exposed mouse. Note that the existence of epigenetic changes does not preclude alterations in the endocrine system as an underlying mechanism. These mechanisms are not mutually exclusive, in that a compound binding a nuclear receptor will ultimately entail changes in gene expression in the nucleus of the cell, which can correspond to an epigenetic mechanism.

1.10 EDs' specific characteristics are recognized by the scientific community at large

It is important to note that there is currently no longer any dispute on the definition of an ED nor on the fact that this class of chemicals induces adverse effects on health and wildlife by interfering with the hormonal system. At a scientific meeting in Berlin in 2016 between epidemiologists, endocrinologists and toxicologists, consensus was reached on the fact that EDs can act at low doses and display non-

monotonic dose response curves (see 1.3.3) without evidence of thresholds below which no effect occurs [98]. In this meeting, the concept of the use of potency with respect to EDs was also discussed and determined as not relevant for ED identification [98].

Another feature of EDs now recognised is the demonstrated vulnerable periods of exposure, often with markedly different tissue sensitivities (see 1.7).

The questions of regulatory issues and requirements that derive from these features are developed in chapters 4 and 5, after some elements on the extent of the impact of EDs on human health, which are presented in the next chapter, and a discussion of the existing ED regulation in the EU (chapter 3).

2 MAIN FAMILIES OF KNOWN AND SUSPECTED ENDOCRINE DISRUPTORS: EVIDENCE FOR WIDESPREAD EXPOSURE AND ADVERSE HEALTH EFFECTS

KEY FINDINGS

- Non-infectious pathologies are causing a huge burden on our societies.
- The diseases and disorders associated with ED exposure are generally multifactorial. However, by using randomization and statistical analysis, toxicological and epidemiological approaches allow disentangling the effects of specific factors. Such approaches have provided demonstrations of actions of specific EDs on different chronic disease outcomes.
- The diseases include obesity and metabolic disorders, male and female reproductive disorders, reproductive cancers as well as thyroid disorders, neurodevelopmental disease and IQ loss.
- Numerous consumer products from cosmetics, toys, furnishings, building materials, cleaning products and food contact materials contain proven and suspected EDs. Human population exposure is widespread, as documented by biomonitoring studies.
- Population impacts and annual costs for seven categories of EDs have been estimated to be over €22 billion with a 95% probability and over €196 billion with a 25% probability in Europe. The largest proportion of costs is related to IQ loss and neurodevelopmental disease.

This chapter deals principally with EDs documented in different products (toys, cosmetics, consumer goods etc). The main suspected or proven health effects of key well-studied EDs are summarized in Table 2 above. Regulations concerning these substances are considered in chapter 3.

2.1 Which methodologies have been used to demonstrate health effects of EDs?

The OECD report updated in 2018 [99], provides a methodological review of the experimental methods (from *in vitro* and *in silico* methods to whole animal tests) that can be used to determine effects of EDs. An overview of the epidemiological approaches used to characterize the effect of EDs on health has also been published recently [100][9].

The Endocrine Society's second statement on ED effects describes the epidemiological and experimental methods that link human and animal exposures, notably during development, to later disease through endocrine disruption [4]. The disorders discussed range from obesity and metabolic disorders, male and female reproductive disorders, reproductive cancers as well as thyroid disorders and neurodevelopment disease and neuroendocrine functions.

[9] Available here: https://www.sciencedirect.com/science/article/pii/S1631069117301294/pdfft?md5=14c2b9f9d6843a7ebed927eb4c009a86&pid=1-s2.0-S1631069117301294-main.pdf

2.1.1 Efficient methodologies to highlight the cause of multifactorial diseases exist

It has sometimes been stated that the multifactorial nature of the diseases and environmental impacts that can be caused by EDs makes the identification of these effects scientifically difficult. As an example, the recent communication towards a comprehensive ED framework [101] mentions that "…there is limited understanding of the specific contribution of chemical exposure and the way to separate it from other possible causes of the negative impacts being investigated. Other factors are indeed also at play in the development of such endocrine-related disorders (such as genetics, nutrition, lifestyle, or other environmental factors) or impacts on wildlife (e.g. overexploitation, climate change);".

However, such general statements misrepresent the nature of the scientific approaches used. It is in the very nature of science to tackle multifactorial phenomena, from the movement of clouds to the occurrence of diabetes or cancer; this is true for physics, economic science, environmental health sciences in general and ED research in particular. Specifically, toxicology tackles complex diseases in several ways, including a *controlled approach* that randomizes animals in the exposed and unexposed groups so as to make sure that the groups are identical with respect to all factors other than the exposure, allowing to discard the role of any other factor. Ecotoxicology combines observations and experiments (e.g. as in the historical example of the DDT effects on egg shell thinning, with, first, observations in wildlife suggesting a role of DDT, and then, experiments showing that the thinning of egg shells can be reproduced with controlled application of DDT) and also allows to study efficiently the web of causation of multifactorial environmental impacts.

For human studies, a randomized controlled approach can generally not be undertaken for proven EDs – although this has in the past been done, e.g. in a randomized control trial with low dose bisphenol A exposure due to drinking from cans [102] or in the case of the effects of a phthalate on male health [103-105]. Here, the main approach used to tackle multifactorial diseases is that the other factors influencing the disease and also possibly associated with ED exposure (the *potential confounders* in the epidemiological terminology) are measured and controlled for by statistical tools such as multiple regression models[10]; see e.g. [100] for more details.

This is not to claim that science has unravelled everything regarding the effects of EDs – for example the exact number of EDs in currently marketed products is not known; neither are all the fine-scale mechanisms implicated in ED effects. Nor is the overall population impact of EDs accurately characterized – just like the overall impact of all carcinogens on health is currently not known. In no case is this a reason to postpone efficient regulation.

There is no lack of tools here – the amount of support to higher education and environmental health research is probably one of the main drivers of the pace of discoveries and of the progress towards a better understanding of whether a given substance is an ED or not. If decision makers need stronger evidence on whether to classify a substance as an ED, one way to achieve this would be stronger support of research (which could be achieved e.g. by finding a mechanism that would make the support to the research on the effects of chemicals dependent on the number of substances marketed). Another option is to enforce stronger test requirements in the application dossiers filed in by the industry (see 3.3.4 and 4.4). This is precisely the logic of the precautionary principle, that calls for action if a strong threat is likely, even in the absence of certainty, with more knowledge generation subsequently confirming or not the threat.

[10] Incidentally, this explains why it would be wrong to state that epidemiology only produces "correlations". In a prospective cohort setting, confounders can be efficiently controlled for and the study allows estimating regression parameters (not coefficients of correlation) that are adjusted for the confounders. Other approaches such as propensity scores can be used to increase the validity of inferences based on epidemiological results.

The approaches highlighted above have allowed identifying EDs in various media and sectors.

2.2 Some suspected EDs present in food contact materials and diet

EDs reported in food packaging (or food contact materials) include bisphenol A, benzophenones and organotins [106]. A data based has been compiled (*Chemicals associated with Plastic Packaging*, or CPPdb [107]) that provides a list of over 906 chemicals associated with plastic packaging and another 3377 likely associated. Food packaging components liable to contain EDs include paper, glue, inks and cardboard. Here we focus on bisphenol A (an ED of particularly high concern for human health), phthalates and perfluoroalkyl substances (PFASs).

2.2.1 Bisphenol A

Bisphenol A was synthesized in 1891 but interest grew after the discovery of its oestrogenic properties in the 1930s, which led to its consideration for use as an oestrogenic drug, until DES, which was more potent in terms of oestrogenicity, was discovered. Instead, bisphenol A was used in the plastics industry. The polymerization of bisphenol A produces polycarbonate, a hard and transparent plastic that is or has been used in various food containers such as water tanks, baby bottles, goblets or other food contact materials. It is also used in the synthesis of polysulfone and polyacrylate. Bisphenol A is also used (at least in EU countries where this use is not banned by national regulations) as an additive in epoxy resins used in the inner coating of food and beverage cans. Bisphenol A is also used as an antioxidant and inhibitor of end of polymerization in polyvinyl chloride plastics (PVC). It has been demonstrated in 1992 that in specific but not unusual conditions (e.g., heating, detergent use…), the polycarbonate polymer molecule can break down into smaller molecules, including bisphenol A monomer, that can migrate to the content of the polycarbonate container. Similarly, bisphenol A from epoxy resins is able to migrate to the food, which constitutes one source of exposure for the general population. In a review written in 2012, it has been estimated that diet is the main source of bisphenol A exposure in humans by an order of magnitude [108], a situation that may have changed since then.

Bisphenol A generates a lot of interest and concern in the scientific community, with over 800 articles published each year in 2014-2018, including 300 per year on the topic "bisphenol A AND health" (source, PUBMED database). We provide here only an overview of the main concerns regarding the health effects of bisphenol A.

At the molecular level, bisphenol A has been shown to be able to interact with an impressive number of nuclear receptors, such as the oestrogen receptors, the orphan receptor human oestrogen-related receptor gamma, ERR , the androgen receptor, the glucocorticoid receptor, the PPAR receptor and to interfere with the thyroid axis. It can also interact with GPR30 (G-protein coupled receptor 30) cellular receptors [109]. Although the strength of the binding of bisphenol A with the oestrogen receptor is much weaker than that of natural (endogenous) oestrogen, this multiplicity of the receptors (some binding to bisphenol A with strong affinity) and signalling pathways that may be activated or influenced by bisphenol A may explain the oestrogenic effects, as well as the large number of biological and health parameters likely to be influenced by bisphenol A at very low doses [110].

The strongest evidence for adverse effects of bisphenol A exposure comes from animal studies. These show or strongly suggest effects of bisphenol A on fat weight, metabolic disorders leading to type-2 diabetes [53, 54], neurodevelopment and behaviour such as hyperactivity [111], reproductive processes [112, 113] and memory performances [114]. Associations with several other outcomes, including gut permeability and learning and memory performance [114], are likely or suspected [110] (see also Table 2).

Regarding cancer, the main concerns relate to breast and prostate cancers. In a review, Seachrist et al. concluded that "Based on the definitions of "carcinogen" put forth by the International Agency for Research on Cancer and the National Toxicology Program, we propose that BPA [bisphenol A] may be reasonably anticipated to be a human carcinogen in the breast and prostate due to its tumour promoting properties" [72].

Because of its very strong variability in the body over time, due to a short biological half-life and repeated exposures throughout the day, bisphenol A is one of the compounds whose health effects are the most difficult to directly characterize in humans, at least with approaches relying on a single biospecimen collected in each subject, a design used so far in most epidemiological cohorts. This strong temporal variability will, on average, lead to a strong under-estimation of the slope of dose-response functions and a decrease in the ability of studies to highlight any effect of the compound, but no increased risk of generating false-positive studies [115]. In spite of this limitation, there is increasing evidence for health effects on bisphenol A directly from human studies, in particular for outcomes such as anxiety in childhood [116-118] and alterations of cardiac or cardiovascular function [102, 119].

Several studies documented effects of bisphenol A at doses assumed safe by regulatory thresholds valid in the EU. Examples include the hypothalamic and hippocampal effects on gene transcription in rats [27], *in vitro* work on mouse and human pancreas showing environmentally relevant levels (exposures in the 1-20 µg/kg body weight/day range) to alter insulin signals [28] and other organ systems [120, 121].

Currently, bisphenol A is banned from food contact materials used for children under age 3 years in the EU; it is not banned for food contact materials in general, so that exposure of pregnant women and foetuses (since bisphenol A crosses the placenta) through diet is still present.

2.2.2 Phthalates

Phthalate esters are a major category of industrial chemicals, with an annual production of probably about 1 million tons per year in Europe. The principal use of phthalates is to increase the flexibility of plastics (e.g. of polyvinylchloride, or PVC). They are found in a plethora of situations and appliances. Examples include toys, medical devices including catheters and blood/saline bags, pharmaceuticals, perfumes and personal care products, paints, printing inks, building materials, detergents, shower curtains and building materials. As phthalates are not bound to their matrix, they can be easily transferred or leach into other substrates. This is notably the case for DEHP [122]. Unsurprisingly, human exposure to phthalates is ubiquitous in EU populations [123-125].

Even though it is not entirely understood how phthalates enter the food chain, a part of human exposure is thought to come from food contact materials [126].

Numerous adverse health effects have been reported for many phthalates. Here we focus mainly on those associated with one of the most used phthalates, DEHP. At the molecular level, DEHP is able to interact with the androgen receptor, eliciting anti-androgenic effects [127]. It can also interact with PPAR receptors and the aryl-hydrocarbon receptor (AhR) [128]. Effects on thyroid signalling are also observed, most likely through effects on the thyroid hormone entry into cells or on thyroid hormone distribution (see references in [129]). No interaction with the thyroid hormone receptor is expected, as the ligand binding domain is highly specific.

Adverse health effects for DEHP have been shown for prenatal exposure and for exposure in childhood. As summarized in

Table 2, multiple studies have demonstrated effects on various reproductive disorders. In animals and humans, prenatal DEHP exposure is associated with reduced anogenital distance in males, an effect consistent with the anti-androgenic properties of DEHP [130](for review of epidemiological studies on phthalate effects on male reproduction see [131]). One of the few prospective human studies with repeated phthalate exposure assessment reported an increased risk of preterm birth in relation to pregnancy DEHP concentration [132]. Another study showed significant association of prenatal exposure with raised oestrogen levels in the mother [133].

Both animal studies and epidemiology have linked phthalates to the developmental neurotoxicity of DEHP (see for instance [134, 135]). Regarding DBP, in adults, a recent experiment reported a possible disruption of the thyroid axis in men following DBP exposure [104].

Some phthalates found in food packaging [107] are classified as EDs within REACH (see Table 6). Consequently, use of four phthalates (DEHP, BBP, DBP and DIBP) will be restricted in consumer products (i.e., authorized only up to a proportion of 0.1% of the weight of the product) as of June 2020[11], a restriction that does not cover use in food.

With increasing restrictions on certain phthalates, those restricted are gradually being replaced by non-phthalate plasticizers. These include Di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), for which adverse health effects have already been reported [136].

2.2.3 Perfluoroalkyl substances (PFASs)

PFASs are primarily used in food contact materials for their water and oil repellent characteristics. That they can migrate into food [137] and increase blood PFAS levels is known and has been underlined in the Madrid statement on PFASs [138]. Intake of fast food was associated with increased levels of different PFASs, including perfluorononanoic acid (PFNA), whereas increased use of canned food was positively associated with perfluorohexane sulphonic acid (PFHxS) [139]. Different PFASs have been reported in pizza boxes and in pre-prepared bags for popcorn [140]. Consumption of fast food has been associated with higher PFAS levels and decreased circulating thyroid hormones [141].

The complexity and the continually changing profile of PFAS production makes it difficult to have an exhaustive characterization of their effects, in addition to the very different metabolism of PFOA between humans and rodents. In spite of this, effects of several PFASs have been identified. These include effects of PFASs on thyroid hormone levels during pregnancy and in childhood [142, 143] and on the thyroid axis [142, 144, 145][12]. With respect to neurodevelopmental disorders, certain longitudinal studies have reported effects of prenatal PFAS exposure on increased hyperactivity, conduct problems and a composite score for autism screening [146] whereas other studies have been less conclusive [147, 148]. In many studies, most of the PFASs measured (up to 16) were present in above 90 % of samples.

Immune responses have also been documented as associated with PFAS levels [149, 150], but whether this implicates an endocrine mechanism remains to be investigated. However, many nuclear receptors are expressed in different immune cells [151]. Hence, the possibility that endocrine mechanisms are implicated should be investigated. Effects on weight gain are also plausible for some PFAS [152], as is an effect of PFOA on ulcerative colitis, an autoimmune disease [153]. Associations of PFOA exposure with kidney and testis cancer incidence in human populations exposed from drinking water following an industrial contamination have also been reported [154]. Effects on liver function have also been reported in humans [155].

[11] https://ec.europa.eu/growth/sectors/chemicals/reach/restrictions_en
[12] See also the evaluation from C8 project regarding thyroid disease: http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Thyroid_30Jul2012.pdf

2.3 Some known and suspected EDs present in cosmetics and personal care products

As underlined by the SSCS in their SCCS/1544/14 memorandum, the regulation of EDs in cosmetics, in this sector identification of EDs is limited by the restriction on animal testing for cosmetic products. Hence it may be particularly difficult to distinguish between a potential ED and a certain ED, if the substance is only registered for use in cosmetic products.

Despite this, there are a number of recognised EDs used in cosmetics and personal care products. Three main classes are briefly covered below.

2.3.1 Parabens

Parabens are a large class of chemicals commonly used as preservatives in many consumer products, including food additives, cosmetics and sunscreens. They have been shown to be exert estrogenic and antiandrogenic activities [156]. Effects on fecundity in rodents have also been reported [157, 158].

Human studies show paraben exposure to be very frequent, with certain parabens also found in amniotic fluid [159]. Few studies on their effects have been conducted in humans so far, which have a limited sensitivity because of the strong within-subject variability of paraben concentrations. Effects on the postnatal growth of boys have been suggested, with parabens maternal levels being associated with an increased weight at three years in boys in two studies [160, 161]. Other epidemiological studies have examined the main types of parabens in pregnant women and their associations with thyroid and reproductive hormones, suggesting changes for methyl and butylparabens [162].

Currently a few parabens have been banned from cosmetics, and this specifically for use on the nappy area of babies and toddlers under the age of three. Other parabens, such as the methyl-, ethyl-, propyl- and butyl-parabens, are considered safe as long as the total paraben content does not exceed 0.4 % content for a single paraben and 0.8 % for mixtures of all parabens in cosmetics. Parabens can modify bisphenol A pharmacokinetics [163].

2.3.2 Triclosan

Like parabens [164] and benzophenones [165], triclosan can be found in amniotic fluid and is found in 98% or more of pregnant women in some populations [124, 166], raising the question of effects arising during pregnancy. Triclosan was first characterized as an ED affecting thyroid homeostasis in 2007 [167]. Triclosan activates hepatic nuclear receptors [168] affecting metabolism and hormone sensitive pathways, notably thyroid hormone levels [169, 170]. High triclosan concentrations were associated with lower thyroid hormone levels [166, 169]

Numerous studies in animal models have detailed adverse effects, including metabolic effects [56, 168]. In humans, a cross-sectional study associated triclosan exposure with increased body mass index [171]. Associations of triclosan levels during pregnancy with reduced head circumference, at least in the male offspring, have been documented in several epidemiological cohorts [161, 172, 173], an association coherent with the ability of triclosan to disrupt the thyroid axis. As for bisphenol A, estimates of association of triclosan with health from human studies based on a spot biospecimen are expected to be underestimated.

In 2016, the FDA banned triclosan use (and that of triclocarban) in consumer soaps, but not in other products. In the EU, the substance is authorized in cosmetics (with a limit concentration).

2.3.3 Benzophenones

As for the previous chemical categories, human exposure to UV filters is ubiquitous, as they are used not only in sunscreens but also as UV-absorbers in a broad range of products, including in plastics to prevent friability [174]. Benzophenones (e.g. benzophenone-1, benzophenone-2, benzophenone-3) are used in sunscreens, with certain being known EDs. For instance, Schlumpf and collaborators screened 9 UV filters for *in vitro* oestrogenic activity. All but one displayed estrogenic activity [175]. As regards the thyroid axis, *in vitro* studies showed five benzophenones to significantly to decrease expression of thyroid-responsive genes [176]. The same study showed benzophenone-1, benzophenone-3 and benzophenone-8 to decrease thyroid hormone levels in an animal model.

Benzophenone-1, benzophenone-3, 4-methyl-benzophenone (4-MBP) and 4-hydroxy-benzophenone (4-HBP) have been detected in amniotic fluid and cord blood samples from Danish populations [165]. Here again, multiple sources of exposure and interactions between chemical classes need to be considered. For instance, both benzophenone-3 and a phthalate (DEHP) were associated with decreased thyroid hormone levels in the NHANES study [177] and in the Danish study cited previously [174]. Given the demonstrated endocrine-disrupting effects of many benzophenones, the risk/benefit of UV filters has been questioned [178].

2.4 Some suspected EDs present in drugs

DES provides a first example of a drug with endocrine-disrupting properties able to induce severe adverse health effects (including congenital malformations and cancer) following intra-uterine exposure [179]. Another relevant example is paracetamol (acetaminophen), which is widely used. Analgesics, including paracetamol and aspirin, are the most widely sold over-the-counter drugs, with increasing trends in the EU since the 1990s [180]. Paracetamol is the most often used drug by pregnant women, who tend to consider that paracetamol is not a drug and is safe for use during pregnancy.

Recent evidence disputes this belief. Paracetamol crosses the placenta, reaching the foetus. Toxicological studies show that it has antiandrogenic properties. In animal models, gestational paracetamol exposure is associated with reduced anogenital distance in male offspring and inhibition of testosterone production as well as interference with prostaglandin production. Some epidemiological studies reported a possible increase in the risk of undescended testes at birth [180, 181]. Adverse effects on girls' development have been reported, including on language development [182, 183].

2.5 Known and suspected EDs present in consumer goods and cleaning products

Today our homes are a major and constant source of EDs [184]. Numerous consumer products such as electronic devices (computers, TV screens, telephones), furniture, upholstery and cleaning products may contain suspected or confirmed EDs. Given these multiple sources, it is not surprising to find that household dust is a source of ED exposure. This is a concern for infants who crawl on the floor and toddlers who tend to put their hands in their mouths.

We discuss specific classes of chemicals and then address issues by sector.

2.5.1 Brominated and phosphorylated flame retardants

To limit fire risk, electronic equipment, furniture covers and mousse and most mattress materials are treated with flame-retardants, many of which are confirmed EDs [185, 186]. Examples include the

polybrominated flame retardants, such as polybrominated diethyl ethers (PBDEs) that have been banned under the Stockholm convention[13] but are still present in household dust [187].

Others still in use include tetrabrominated bisphenol A (TBBPA) and the more recently introduced phosphorylated flame-retardants. Members of each group have been shown in experimental and epidemiological studies to interfere with thyroid hormone signalling and, in many cases, as a consequence, with brain development and neurodevelopmental disease. More specifically, PBDEs have been linked in longitudinal studies to IQ loss and increased risk of Autism Spectrum Disorders and ADHD [188-190]. PBDEs have also been associated with reproductive disorders [191, 192], TBBPA with adverse thyroid hormone and neurodevelopmental effects in rats [193] and phosphorylated forms with thyroid homeostasis [194, 195].

2.5.2 Phthalates

Besides their use in perfumes and personal care products, phthalates are commonly used in cleaning agents [196]. As the ED properties of this chemical class have been developed above (see 2.2.2), they are not reiterated here.

2.5.3 Perfluoroalkyl substances (PFAS)

Besides often being treated with flame-retardants, carpeting and upholstery (e.g. curtains) can also be treated with polyfluoroalkyl substances (PFASs) or surfactants to waterproof them and render them "spill-resistant". Two categories of PFASs, perfluorooctanoic acid (PFOA, also known as C8) and perfluorooctane sulfonic acid (PFOS), are of particular concern as they are exceptionally persistent and can bioaccumulate. These compounds are found in human blood, cross the placenta and are found in amniotic fluid. Their half-life in humans (the time to eliminate 50% of the load) is four to five years. The health effects of PFASs were developed in 2.2.3.

The application of REACH regulation introduced restrictions on PFAS in 2017 and included several derogations for different industrial sectors and uses. It will apply from 2020[14].

The EPA has instigated a number of actions on PFAS[15]. In 2010/2015 they asked manufacturers of PFASs to complete of the phaseout of one of the major compounds of the family, PFOA. However, as changes in production resulted, serum concentrations of others PFASs has increased, including perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), with some estimates placing the number of PFASs at several thousands [16]. Independently of household use, PFAS surfactants are widely used in food contact materials (see section 2.2.3) and firefighting foams. Significant, health-endangering PFAS contamination of water supplies near military bases using PFAS-based foams was reported in Sweden [197].

2.5.4 Cleaning products

Many cleaning products intended for use in bathrooms and kitchens can also contain known and potential EDs, e.g. nonylphenols, parabens, phthalates and glycol ethers.

The France-based PELAGIE cohort (see [198-201]) has highlighted groups of ethyl glycols as ED candidates. These epidemiological studies have demonstrated associations between maternal levels of certain glycol ethers, notably methoxyacetic acid (MAA) and risk of cryptorchidism and hypospadias

[13] http://chm.pops.int/Implementation/NIPs/Guidance/GuidancefortheinventoryofPBDEs/tabid/3171/Default.aspx
[14] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1000&from=EN
[15] https://www.epa.gov/pfas/epa-actions-address-pfas
[16] https://www.epa.gov/sites/production/files/2018-11/documents/cecs-pfcs-factsheet.pdf

[199]. Other studies on this cohort showed that phenoxyacetic acid (PhAA) levels in cord blood were associated with lower sex steroid and steroid hormone binding globulin (SHBG) in boys and with higher SHBG levels and certain steroids in girls. Two other glycol ethers displayed associations with oestradiol levels. As the authors conclude, given the data on glycol ether exposure and time to pregnancy [201] and neurocognitive performance [200], maternal exposure to these compounds is cause for concern.

Nonylphenols were amongst the first oestrogenic EDs identified [202]. They are commonly found in detergents and other consumer products. Although weak, the oestrogenic activity of nonylphenol has been associated with various ED related adverse outcomes including breast cancer [202] and fertility problems in men [203] and women [204]. Exposure to nonylphenol during pregnancy has been associated with smaller gestational weight and shorter offspring length [205].

2.5.5 Building materials

Other than the flame-retardants and surfactants described in 2.5.1 and 2.5.3, different construction materials contain significant levels of known or suspected EDs [206]. Examples include polyvinylchloride (PVC), used in floor coverings is associated with increased phthalate exposure [207, 208], PCBs widely used, prior to their ban, for electrical and general building insulation [206].

2.5.6 Medical Devices

Some medical devices contain EDs or suspected EDs, which is of particular concern if the EDs are on a part of the device in contact or within the body. One of the most difficult situations is care of premature babies. This exceedingly vulnerable population is highly exposed in intensive care situations, notably to phthalates from polyvinylchloride (PVC) tubing. Estimates have placed exposures up to 160,000 times above safe levels [209].

2.5.7 Toys

Phthalates are well-documented EDs found in many flexible plastic toys [210]. Banned phthalates have been reported to be present above permitted levels in 20% of toys inspected[17]. Other EDs including bisphenol A [211] can also be present. Exposure can occur directly or indirectly through household dust [212]. See 3.6.1 for discussions about the regulation.

2.6 Some known and suspected EDs present in pesticides

In 2013, EFSA published a report showing that of 287 currently-marketed pesticides, 101 affected thyroid signaling at some level [213], displaying potential ED properties. Another 97 showed neurotoxic effects. This latter finding raised questions as to the efficacy of the plant protection products and biocide evaluations. In the same vein, in late 2018, it was revealed that the chlorpyrifos documents submitted by the manufacturer to the regulatory authorities had underestimated the effects of exposure on brain parameters [214]. These discrepancies were ignored by the agencies evaluating the dossier in the USA and in the EU. These facts underline the importance of thorough review of pesticide data. They also contribute to explaining the large cost in terms of IQ and neurodevelopmental disease risk associated with prenatal chlorpyrifos and other organophosphate pesticides exposures [215] (see section 2.8).

These currently insufficiently tested plant protection products and biocides add to the effects of banned ED pesticides. These "legacy pesticides" are still present in human fluids, long after production has ceased due to their persistence. The list includes lindane, chlordane, DDT and hexachlorobenzene (HCB).

[17] https://echa.europa.eu/fr/-/inspectors-find-phthalates-in-toys-and-asbestos-in-second-hand-products.

Numerous other plant protection products or biocides have been described as known or suspected EDs; see for instance [216-218] and The Endocrine Disruption Exchange (TEDX) list which includes pesticides [18], as does the EU Commission's Impact Review for the implementation of the plant protection products regulation and biocidal products regulation[19].

Below we focus on four categories of pesticides of major current concern.

2.6.1 Organophosphate pesticides

A recent publication [219] underlined how the widespread use of this category of pesticides has led to ubiquitous human contamination that are compromising children's mental health through effects on brain development. Of particular concern, is chlorpyrifos, exposure during pregnancy, which has been associated with IQ loss, thinner brain cortex and increased neurodevelopmental disease risk including ADHD and autism spectrum disorders. The ED effects of chlorpyrifos have been shown multiple times, but recent evidence of its thyroid disrupting potential on developing coral fish (and hence on other vertebrates including humans) is among the most detailed and disquieting [220].

2.6.2 Triazoles and other fungicides

Many fungicides exert ED effects, including bifonazole, imazalil, and flusilazole, that have been shown to inhibit aromatase action purified from human placenta [221]. Other mechanisms of action include inhibition of thyroid peroxidase [170], a factor that will affect thyroid hormone production.

Other fungicides have been shown to affect multiple aspects of endocrine signalling (see for example [222-226]). Examples of fungicides with anti-androgenic properties include prochloraz (an imidazole) [227] and procymidone [228].

2.6.3 Pyrethroids

Pyrethroids, derived from chrysanthemum plants, have increasingly been applied as alternatives to organophosphate pesticides and are now the fourth most used pesticide category world-wide [229]. As a result, there is wide scale contamination of rivers, and as a consequence, fish. Work on fish and mammalian models, as well as human epidemiology studies show multiple endocrine disrupting effects of different pyrethroids [229-232].

2.6.4 Neonicotinoids

Much current concern focuses on the effects of neonicotinoids on insect, notably bee, populations [233, 234], with obvious socio-economic consequences. However, many mammalian studies have linked this pesticide class with ED activity, notably on placental aromatase activity [235]. A recent report using an *in vitro* cell-based assay showed significant ED effects of one neonicotinoid on adipose cells [236].

2.7 Biomonitoring data on EDs and suspected EDs

As a result of the past or current use of suspected EDs in the above-mentioned sectors, ED presence can be highlighted in the environment, in various media including diet and in humans. For a large proportion of the suspected EDs that have been assayed in EU population, most subjects are exposed, as documented by biomonitoring studies.

[18] https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/updates
[19] https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/2016_impact_assessment_en.pdf

2.7.1 In diet

In a few EU countries, detailed monitoring of the contamination of food by chemical substances (including suspected or proven EDs) have been performed using a rigorous sampling design and assessing a large number of chemicals. For example, for France, Anses performed studies of the total diet (TDS, total diet studies[20]) in 2000-2004, 2006 and 2011; the latter survey focused on the diet of children until 3 years of age. In this survey, the concentration of 670 chemicals were assessed in almost 5500 food samples covering most of the diet of children below 3 years and collected in all French regions. In addition to the assessment of exposure levels (based on actual food patterns in children), Anses performed a risk assessment for each of the chemical considered separately, taking into account any existing dose-response function relating exposures to adverse effects, when available. The study found detectable levels in the food of children until age 3 for several proven or suspected EDs, such as PCBs, methylmercury, genistein (for children using soy-based products), benzophenone, bisphenol A (at a time when it was still authorized in food contact materials for children), perfluoroalkyl substances including PFOA and PFOS, PBDEs, and a large number of pesticide residues. For some of these substances, a health risk could not be discounted, based on dose-response functions from the literature.

2.7.2 In human populations – data available at the EU level

In 2017, the first results of one of the main "exposome" projects funded by the EU, Helix early-life exposome projects, provided an assessment of the levels of 45 chemicals circulating in the bodies of pregnant women from six EU countries (pregnant in 1999-2010) and their children. The assessment of the levels of chemicals in blood and urine was done in a central laboratory ensuring high quality. Among the 45 chemicals assessed, several were either officially recognized EDs (bisphenol A, DEHP...) or suspected EDs such as other phthalates, perfluorinated compounds, mercury and metabolites of organophosphate pesticides. In 90% of children and of their mothers, at least two thirds of the investigated substances had detectable levels (see Table 3). Over 90% of children, in whom samples were collected in 2013-2016, had detectable levels of several PCBs, of DDE (a DDT metabolite), PBDE-47, several perfluoroalkyl substances including PFOA and PFOS, several phthalates including DEHP metabolites, parabens such as methyl- and ethyl-parabens, triclosan…

Such data are informative and confirm the widespread exposure, to varying concentrations, to a large number of EDs or suspected EDs in children and pregnant women, although, because of the focus limited to a few EU cities and of the lack of random sampling frame, they cannot be used to provide a representative estimate of exposures of the EU population. To our knowledge, there is currently no biomonitoring study available with EU-wide implementation of a harmonized population sampling on a specific population (e.g., pregnant women or children from a specific age-group) covering a large number of EDs.

2.7.3 In human populations – data available in specific countries

Detailed information about exposure to chemicals, including EDs, exist in specific countries such as Belgium [237], France [238], Germany, where compounds such as phthalates have been monitored for a long time [125] and Portugal [239]…

As already mentioned, it is by combining the dose response functions controlled for confounders issued from epidemiological studies for EDs with the highest likelihood of an effect with the type of biomonitoring data that we just described that an estimate of the population impact of EDs can be obtained.

[20] https://www.anses.fr/en/content/total-diet-studies-tdss

Table 3: Distribution of urinary or blood concentrations of chemicals in 1300 EU children from Helix exposome project. P25, P50, P75: 25th, 50th (median) and 75th percentiles [124].

		Maternal samples						Child samples					
Compound		P25	P50	P75	Max	n analyzed	% quantifiable samples	P25	P50	P75	Max	n analyzed	% quantifiable samples
PCB 118	ng/g lipid	1.57	2.64	4.82	39.0	829	79.1	1.51	1.98	2.94	134	1279	99.8
PCB 138	ng/g lipid	5.54	9.10	16.1	132	1048	96.5	3.36	5.37	8.70	215	1279	99.8
PCB 153	ng/g lipid	10.4	17.6	30.5	214	1048	99.6	7.28	11.6	18.6	217	1279	100
PCB 170	ng/g lipid	1.84	3.69	7.06	84.5	826	99.5	0.56	1.26	2.75	27.5	1279	90.7
PCB 180	ng/g lipid	5.78	10.4	18.6	201	1048	97.6	1.62	3.68	8.02	62.5	1279	99.2
DDT	ng/g lipid	0.82	1.33	3.06	94.1	826	65.6	0.28	0.71	1.65	198	1279	79.8
DDE	ng/g lipid	25.9	52.3	111	1903	1048	99.9	11.6	21.8	45.6	2158	1279	100
HCB	ng/g lipid	5.59	8.16	13.0	164	1048	99.1	6.27	8.19	11.4	88.1	1279	99.9
PBDE 47	ng/g lipid	0.27	0.43	0.75	34.74	684	80.8	0.15	0.23	0.37	41.7	1279	90.8
PBDE 153	ng/g lipid	0.03	0.45	0.66	198	648	72.9	0.03	0.16	0.42	16.5	1279	54.4
PFOA	µg/L	1.38	2.30	3.34	31.6	1240	99.7	1.19	1.55	1.97	6.66	1301	100
PFNA	µg/L	0.43	0.69	1.08	5.92	1240	97.9	0.30	0.47	0.72	11.5	1301	99.5
PFUnDA	µg/L	0.10	0.19	0.29	2.80	1032	95.4	0.02	0.03	0.09	1.51	1301	68.6
PFHxS	µg/L	0.31	0.55	0.91	21.0	1240	97.5	0.19	0.36	0.61	28.5	1301	99.7
PFOS	µg/L	4.12	6.41	9.63	48.0	1240	100	1.26	2.03	3.22	33.8	1301	99.8
As	µg/L	0.28	1.19	2.27	90.1	833	58.5	0.28	1.37	2.34	63.6	1298	67.1
Cd	µg/L	0.15	0.22	0.33	27.9	833	99.6	0.04	0.07	0.09	1.79	1298	86.5
Cs	µg/L	1.19	1.56	2.15	10.9	833	100	1.04	1.38	1.77	8.37	1298	100
Hg	µg/L	0.98	1.90	3.45	43.5	1020	98.9	0.42	0.86	1.75	20.1	1298	97.7
Pb	µg/L	7.14	9.66	13.20	187	833	100	6.39	8.53	11.1	213	1298	100
Tl	µg/L					833	1.1					1298	7.2
MEP	µg/g creat.	72.0	179	469	17,733	1080	99.0	16.4	33.5	76.4	3197	1301	100
MiBP	µg/g creat.	23.3	38.7	60.7	705	1088	99.9	25.9	41.8	73.3	861	1301	100
MnBP	µg/g creat.	18.3	29.6	47.3	6445	1089	100	15.3	23.9	38.3	488	1301	100
MBzP	µg/g creat.	3.63	7.33	15.3	775.1	1088	99.7	3.00	5.00	8.51	351	1300	99.9
MEHP	µg/g creat.	4.42	8.73	15.3	417	1085	99.5	1.70	2.88	5.10	282	1260	96.8
MEHHP	µg/g creat.	10.5	18.2	31.2	967	1089	100	12.2	20.1	33.2	2241	1298	99.8
MEOHP	µg/g creat.	8.29	14.1	23.7	783	1089	100	7.66	12.5	20.8	1289	1300	99.9
MECPP	µg/g creat.	22.4	33.6	52.3	1361	913	99.9	21.5	35.1	59.5	3681	1300	99.9
oh-MiNP	µg/g creat.	0.61	0.91	1.47	66.5	914	92.6	3.38	5.36	9.26	548	1301	100
oxo-MiNP	µg/g creat.	0.62	1.03	1.75	75.1	914	95.7	1.86	2.83	4.87	680	1301	100
MEPA	µg/g creat.	39.5	167	389	39,241	815	99.8	3.28	6.50	26.4	23,963	1299	99.7
ETPA	µg/g creat.	1.14	6.26	26.72	6774	817	97.4	0.43	0.67	1.22	2033	1298	99.3
PRPA	µg/g creat.	8.87	44.2	134	12,463	1083	97.3	0.02	0.22	1.68	1758	1284	67.3
BUPA	µg/g creat.	0.36	3.37	14.4	371	1083	97.0	0.04	0.08	0.16	96.8	1296	96.6
BPA	µg/g creat.	1.55	2.82	6.60	107	1084	99.4	2.42	4.06	7.17	362	1289	98.3
OXBE	µg/g creat.	1.46	4.90	27.5	12,837	1085	99.3	0.86	2.16	6.96	7985	1301	99.9
TCS	µg/g creat.	1.50	6.28	79.9	1653	1085	98.5	0.32	0.61	1.50	702	1301	100
DMP	µg/g creat.	4.13	8.37	16.4	321	1080	90.8	0.29	0.78	4.70	83.3	1295	49.3
DMTP	µg/g creat.	2.05	4.96	12.4	220	1084	88.9	1.27	2.99	6.50	405	1300	90.4
DMDTP	µg/g creat.	0.05	0.19	1.54	134	969	41.6					1300	18.2
DEP	µg/g creat.	1.86	3.33	6.44	198	1082	97.8	0.47	1.83	4.52	665	1299	80.9
DETP	µg/g creat.	0.12	0.58	2.56	44.3	1037	50	0.10	0.18	1.72	78.5	1280	43.5
DEDTP	µg/g creat.					1084	1.7					1301	1.5

BPA: Bisphenol A. BUPA: Butylparaben. DDE: metabolite of the DDT insecticide. DMP, DMTP… DEDTP are organophosphate pesticide metabolites. HCB: Hexachlorobenzene (organochlorine pesticide). ETPA: Ethylparaben. MEP, MiBP, MnBP, MBzP, MEHP…oxo-MiNP are phthalates metabolites, with MEHP, MEHHP, MEOHP and MECPP being DEHP metabolites. OXBE: Oxybenzone. PCB: polychlorinated biphenyls. MEPA: Methylparaben. PBDE: Polybrominated flame retardants. PFOA, PFNA, PFUnDA, PFHxS, PFOS are perfluoroalkyl substances (PFASs). PRPA: Propylparaben. TCS: Triclosan.

2.8 Available estimates of population impact

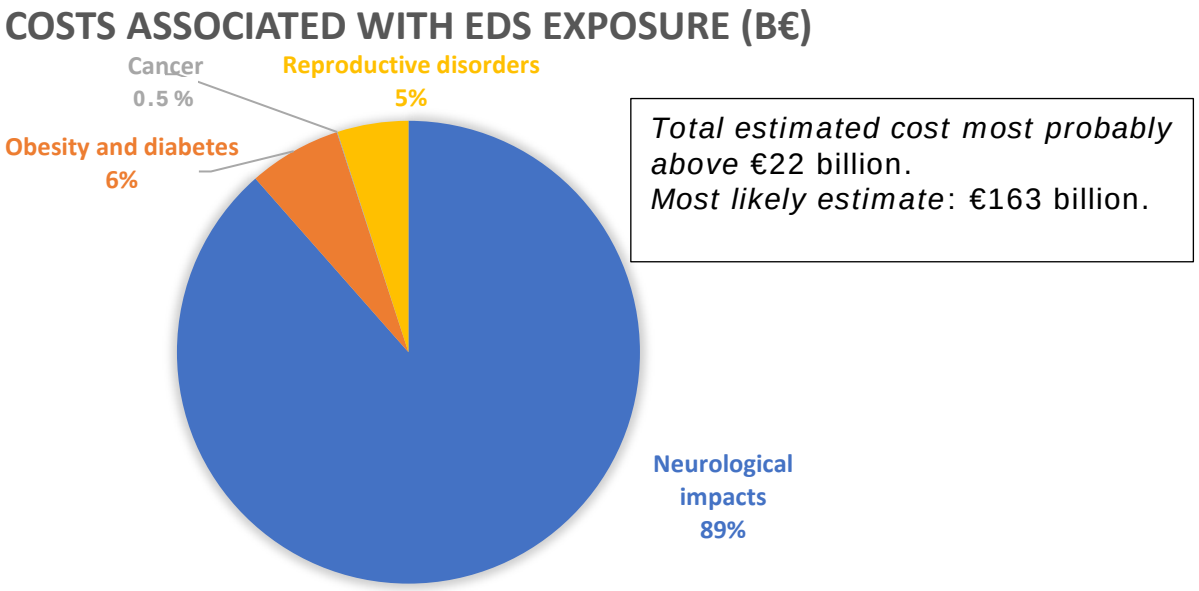
2.8.1 Results of Trasande et al. costs estimate

A series of recent studies have attempted to provide an impact of the risk associated with exposure to EDs, following the logic of Figure 11. Generally, such studies are limited by the facts that a) efforts to identify EDs have been so far limited, relative to the total number of substances present in the environment or marketed in the EU; b) by the limited availability of dose-response functions relevant for human populations; c) by the limited amount of harmonized data on ED population exposure at the scale of the EU (see above); d) by the limited availability of data on the healthy (or disability-adjusted) life-years lost (DALYs) and tangible and intangible costs relative to diseases that may be induced by ED exposure.

This does not preclude commenting the few available studies, since it is in some cases possible to anticipate the direction of the impact of these uncertainties on the results.

In 2015-2017, Trasande et al. published a series of studies aiming at estimating the health and economic costs "that can reasonably be attributed to endocrine disrupting chemicals exposure in the EU" [240, 241]. With some adaptations, the methodology relied on the classical methodology of attributable fraction, which requires information on a measure of exposure level to each compound of interest and an estimate of the dose-response function(s) for all health outcomes influenced by each compound. To the extent that the dose-response functions issued from epidemiological studies are adjusted for the main confounders, such an approach does not suffer from bias due to the existence of other causes of the diseases considered, including genetic factors, which are very unlikely confounders in such studies.

Figure 12: Estimated costs associated with exposure to endocrine disruptors in the EU, following a weight of evidence approach; from [240].



Costs were estimated by multiplying the number of disease cases attributable to ED exposure with the unitary cost associated with each disease. An important feature of the study was the approaches used to account for uncertainties. Authors relied on a *weight of evidence* approach allowing to weight the cases and costs associated with the health events attributed to a given exposure by the level of evidence of the dose-response function relating the exposure and the outcome. The framework for evaluating the level of evidence consisted in combining the probability of causation based on toxicological and epidemiological studies. To illustrate this, if there is some evidence that ten different EDs cause specific diseases, with a cost, considering the dose-response functions and exposure levels to each ED, evaluated to €100 M for each endocrine disruptor and disease, but that the level of evidence for these effects was about 50% (that is, the level of scientific evidence is far below certainty), then the total cost considered for these 10 EDs and diseases in the study would have been €500 M. Such a weight of evidence approach allows avoiding the pitfall of considering only effects with a very high level of evidence (which is expected to underestimate impacts) without falling into the opposite pitfall of taking for granted all associations that have been reported in the literature, sometimes with poor designs.

The estimated costs related to the effects of exposure to the considered EDs was €163 billion per year (Figure 12), with a 95% probability that costs were above €22 billion and a 25% probability of costs at least €196 billion/year [240].

An important additional conclusion to draw from this study is the limited availability of data on the body burden of EDs in the EU population. This, and the lack of consideration of EDs effects whose plausibility increased since these costs were estimated (see below) argue, if anything, for underestimation of costs, although extensive EU-wide biomonitoring, as well as additional cohort studies would be warranted to precisely confirm all assumptions of the Trasande et al. studies.

Table 4 provides a comparison of these estimates with available estimates of the effect of other environmental and lifestyle factors, showing that the current ED cost estimates, even though they are possibly underestimations, would correspond to approximately 30% of the costs incurred by smoking the EU.

Table 4: Estimated costs incurred yearly in the EU by various lifestyle or environmental factors. See above for discussion.

Factor	Estimated cost, EU (Billion €)	Year of estimate and reference
Smoking	544	https://www.erswhitebook.org/chapters/tobacco-smoking/societal-costs-of-smoking/
Atmospheric pollution ($PM_{2.5}$)	704	(WHO)
Endocrine disruptors*	163	2015 [240]

2.8.2 Published criticisms of Trasande et al. costs estimate

To our knowledge these studies have not been criticized by independent researchers and no contradicting cost estimates from independent researchers have been published.

The Trasande et al studies were criticized in a commentary first authored by a consultant with ties to the American Chemistry Council [242] and in two succinct letters addressed to the editor of Journal of Clinical Endocrinology and Metabolism. The letters criticized the paper on IQ loss and neurodevelopmental disease (Attention deficit/hyperactivity disorders and Autism), which found the highest costs [215], and the female reproduction study [58]. As to the actual letters, in each case, one of the two authors had ties to industry. Trasande and colleagues published argued replies to each letter[21].

In the paper by Bond and Dietrich [242], several concerns were voiced using terms such as "alleged costs" and insufficiently "adequate scientific scrutiny". The criticisms seem to have been undertaken with the assumption, "given the aggressive media campaign that accompanied the Trasande et al. (2015) publication", that the study "may have biased the results toward exaggerating costs". This *a priori* assumption by Bond and Dietrich might explain why specific limitations that might have led to an underestimation of costs were not addressed in the criticisms.

Another criticism related to the strength of evidence for the effects of polybrominated flame retardants (PBDE) and of organophosphate pesticides on child IQ, and the lack of reliance on a systematic review methodology in assessing the overall epidemiological evidence on the topic.

[21] https://academic.oup.com/jcem/article/100/6/L54/2829568
https://academic.oup.com/jcem/article/101/11/L110/2765052

Similarly, Bond and Dietrich [242], questioned the strength of evidence for organophosphate pesticides effects on IQ. They examined the data on chlorpyrifos and cite a series of articles most of which are (co)-authored by consulting groups linked to industry. The only one that is authored by academics concluded in 2008 that " further investigation is needed" , as are "more rigorous measures of exposure" [243].

Trasande et al. considered longitudinal cohort studies available for prenatal exposure to chlorpyrifos in relation to IQ. Since then, further experimental animal evidence as to the ED effects of chlorpyrifos on thyroid hormone, a hormone essential for brain development, has appeared [220]. In addition, a publication has shown [214] that the manufacturers' file submitted for chlorpyrifos authorisation was deliberately misleading, notably for exposure effects on brain development, which were significant. Effects of prenatal organophosphate exposure on IQ loss have been further documented in a longitudinal human study [244]. Similarly, a recent review of exposure during pregnancy to organophosphate pesticide use and brain disorders has been published [219]. Importantly, a *natural experiment* occurred when a ban on household use of chlorpyrifos was introduced. Before the ban, decreases in birth weight and length in relationship to levels of chlorpyrifos were seen in newborn cord blood, associations no longer seen after the ban [245].

As to the effects of PBDE on IQ, since the publication of the Trasande et al. studies, a systematic review of the evidence regarding PBDE exposure and IQ was published. It concluded that the level of evidence for an effect of PBDE on IQ, based on epidemiological studies, was *sufficient* [246], which can be seen as consistent with the assumption by Trasande et al. who proposed that the strength of the human evidence regarding this association was *moderate to high*.

Regarding dose-response functions in general, it can further be stated that, for the non-persistent chemicals considered (such as organophosphate pesticides), the epidemiological studies used, which so far almost exclusively rely on spot biospecimens, are expected to provide under-estimates of dose response functions for the least persistent compounds [115, 247].

One general criticism from Bond and Dietrich [242] related to the fact that the study was overseen by a "steering committee that consisted of self-appointed group of eight scientists who have published research and actively engaged in public policy advocacy on the topic of [EDs]." However, each of the individual studies were written by experts in the different fields, principally academic researchers who stated if they held conflicts of interest and each of whom had clear publication and funding track records on the relevant topics under study. Despite the criticism suggesting a collusion by scientists, Bond and Dietrich suggest no alternative method to the rigorous selection criteria for participation used by Trasande et al. Also, in their critique, Bond and Dietrich cite evidence that mixes adult exposure with prenatal exposure, thus ignoring the well documented windows of vulnerability for exposure and underestimating effects.

In addition, one can note that the level of evidence for several dose-response functions not included in the Trasande et al. evaluations, and corresponding to chemicals with widespread exposure, was strengthened since this publication, e.g. regarding the implication of bisphenol A in prostate cancer or breast cancer [72] and of prenatal DDT exposure for breast cancer [11] and childhood obesity [248].

Overall, Bond and Dietrich [242] offered no alternative method for cost estimate, and their arguments confounded prenatal and adult exposures. Further, since the Trasande et al publications, multiple studies show documented levels of prenatal ED exposure to affect IQ and other adverse health outcomes (see references above). For a further discussion of cost criticisms see Annexe 3 page 102.

2.9 Limitations of the current regulatory risk assessment framework to minimize ED exposure and efficiently protect health

2.9.1 Current regulatory framework for the management of chemicals

In some sectors for which human exposure can be expected, chemicals in general and EDs in particular are managed under a logic that requires identification of thresholds. These refer to the concepts of predicted no effect concentrations (PNEC), derived no effect level (DNEC, both used in the context of REACH regulation) or no observed adverse effect levels (NOAEL). This logic is currently applied e.g. in the sectors of REACH chemicals, at least for substances not recognized as carcinogens, mutagens or reprotoxicants.

It is important, following Slob et al. (cited in [249]), to distinguish several types of thresholds, and in particular:

- Biological thresholds: The dose below which the organism does not suffer from any [adverse] effects from the compound considered.
- Experimental thresholds: The dose below which no effects are observed using specific tests.

These are in addition to *regulatory thresholds*, e.g., the maximum exposure tolerated in a population.

The biological threshold is expected to depend on many parameters, such as existence of subjects with heightened sensitivity to the compound in the population, e.g. because of a sensitive stage of development, of specific tissue sensitivities, of existing diseases or altered detoxification of reparation mechanisms.

As noted in 2013 following a meeting convened by the JRC [249], experimental approaches cannot demonstrate the existence of thresholds, as it is generally scientifically not possible to demonstrate that something does not exist (in this case, that there is no difference in disease occurrence between a group not exposed to the chemical of interest and a group exposed to a very low dose). It is by biological considerations that one may dispute the plausibility of the substance acting at extremely low doses, which requires very detailed knowledge on its mechanisms of action.

When it comes to the risk management of the chemicals, as recalled by the JRC:

> "The current risk assessment paradigm follows one of two approaches; either assuming a biological threshold exists and taking the experimental NOAEL/NOEC or benchmark dose from the critical study as being a dose level at which there is a small response level and incorporating a number of uncertainty or variability factors to derive an acceptable (by society) exposure level; or in the case of genotoxic carcinogens and germ cell mutagens, being unsure about whether or not a biological threshold exists and that even if an experimental NOAEL were to be available, it has to be considered inappropriate to derive an acceptable exposure level by applying the same methodology used for threshold effects. The latter approach leads in many regulatory domains to risk management measures by removing the substance from the market or, if not possible, by reducing exposure to as low as achievable. In the case of genotoxic carcinogens this so-called non-threshold approach has as its historical origins the premise that even one molecule could cause one irreversible mutation which could be the starting point of an eventual malignant tumour."

2.9.2 The "threshold" debate

The previous paragraph provides insight as to why a part of the debate between some toxicologists from the chemical industry and academic toxicologists focused on the issue of whether EDs effects on health

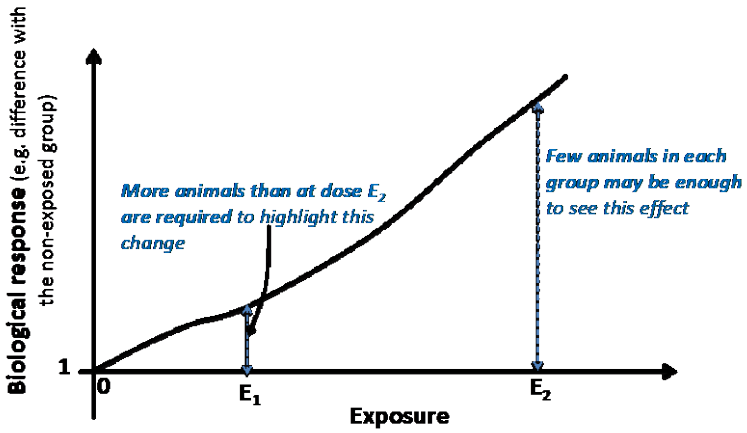
follow a dose-response function with a threshold. If the existence of a biological threshold is unlikely, as for carcinogens, then EDs should be managed according to a logic of strong restrictions or ban (no exposure or exposure minimization). If the existence of a biological threshold is plausible, then there would be no need to lay down specific risk management procedures for this class of hazard, but simply to identify it using relevant tests as is done for the other hazard classes. This logic assumes that, if a biological threshold exists, the tests commonly used allow to estimate them accurately.

2.9.3 Are existing test methods sufficiently sensitive?

Available evidence suggests that currently used tests are, in general, inefficient to identify effects of the test substance occurring environmentally-relevant doses (i.e., poor sensitivity of tests).

The current approach to threshold identification in regulatory toxicology does not equate *experimental thresholds* with *regulatory threshold*, in that a number of safety factors (also termed *uncertainty factors*) are applied to the experimental threshold to obtain the regulatory threshold. Thus, a factor of 100 may be applied to the experimental threshold to obtain the regulatory threshold. These safety factors are meant to take into account uncertainties related to the interspecies extrapolation, and to the variability of sensitivity within human populations, but are not meant to compensate other technical limitations of the test, such as limited power, interpretation of lack of observed effect as evidence of lack of effect, insensitive outcome or animal strain, etc.

Figure 13: Illustrations of the decreased sensitivity of regulatory tests for a given number of animals in each compared group, in the hypothetical situation of a compound with a monotonous effect**.** Generally, test methods do not require the number of animals compared to increase as the tested dose decreases. As the tested exposure decreases, the probability to detect an effect decreases, so the test could conclude the existence of a threshold at exposures for which an effect may still exist.



As recalled in the JRC report [249], "It was also highlighted that the experimental NOAEL/NOEC is not equivalent to the true biological threshold but rather reflects the limit of detection of the method for that endpoint, regarding statistical power to detect an effect as well as the inclusion of relevant sensitive endpoints." The issue of statistical power (defined as the probability to highlight an effect if there is one) refers to issues such as (i) the habit to interpret a "non-significant" test (corresponding to a p-value above a threshold of usually 0.05) as evidence of a lack of effect (while it generally should only be seen as lack of evidence of an effect), and (ii) reliance on a rather small number of animals in the compared groups. We illustrate the issue of statistical power in Figure 13. Even assuming a linear dose-response function, these issues related to statistical power would warrant an increase in the number of animals or observation

units as the dose decreases (to magnify the sensitivity of the test at this dose), an approach which is to our knowledge not generally used. Such an approach would go against the aim of limiting animal experiments.

Thus, generally, in spite of the use of "safety factors", experimental thresholds are probably not conservative estimates (i.e., they are not very protective). This is illustrated by the fact that, over the years, as newer more sensitive tests are developed and academic research is conducted, the *regulatory* thresholds of compounds tend to decrease. For example, the EU tolerated daily intake of bisphenol A was decreased from 50 µg/kg body weight/day in 2011 to 4 µg/kg/day in 2015 (a value considered to be too high by some regulatory agencies and many scientists). For this reason, this "safe thresholds" approach may be deemed acceptable for rather limited hazards, that is, for health effects leading to rather minor or curable diseases. However, this approach is less advisable for more serious health effects with fewer therapeutic options, such as cancer or neurodevelopmental troubles. It would also be in agreement with the precautionary principle not to accept an approach that is not totally efficient in identifying safe thresholds for carcinogens or EDs. Such a logic prevailed e.g. in the plant protection products (PPPR) and biocides (BPR) regulations, that do not rely on the identification of "safe thresholds" for the hazards of highest concerns, namely CMR substances and EDs (see 3.2.1).

In the case of EDs specifically, further limitations to the "safe threshold" approach exist. These relate (i) to the sensitivity of the biological outcomes considered by the tests used in regulatory toxicology for EDs, such as those validated by OECD guidelines. One of these tests, the uterotrophic assay, for example focuses on the organ weight; although a change of the weight of an organ may be the sign of toxicity, many toxic effects are exerted by subtle mechanisms that do not entail any change in the overall organ weight (see [250] for an example) ;(ii) to the variability of some of the main tests used; regarding again the main test used to detect oestrogenic effects, the uterotrophic assay, which relies on changes in uterus weight in mice or rats models, its results have been shown to depend on variations in protocol within the guidelines, such as the choice of rats or mice, or the exposure route (injection *versus* gavage), which are all permitted by the guidelines [251]; (iii) to the likelihood of a monotonic dose response function generally assumed in regulatory testing, which is an unlikely default assumption for most EDs [25]; (iv) to the lack of consideration of combined exposure to many other possible EDs in the identification of safe thresholds (see 1.6.2), some of which are expected to influence the same outcome or act on the same pathway as that influenced by the considered chemical; and most importantly (v) to the biological knowledge about the mode of actions and EDs, that are expected to act at very low doses (see 1.3.2).

In other words, these methods will, for the methodological limitations outlined above, generally identify experimental thresholds, but these will in no way constitute a strong evidence for the existence of a biological threshold. These test thresholds are expected to provide a poor identification of the dose range where any effect would be very rare for EDs.

These considerations on biological and regulatory thresholds, at the frontier between science and regulation, lead us to the description of the current regulatory framework of EDs in Europe.

PART B: MANAGING THE RISK INCURRED BY EDCs – WHAT IS CURRENTLY DONE

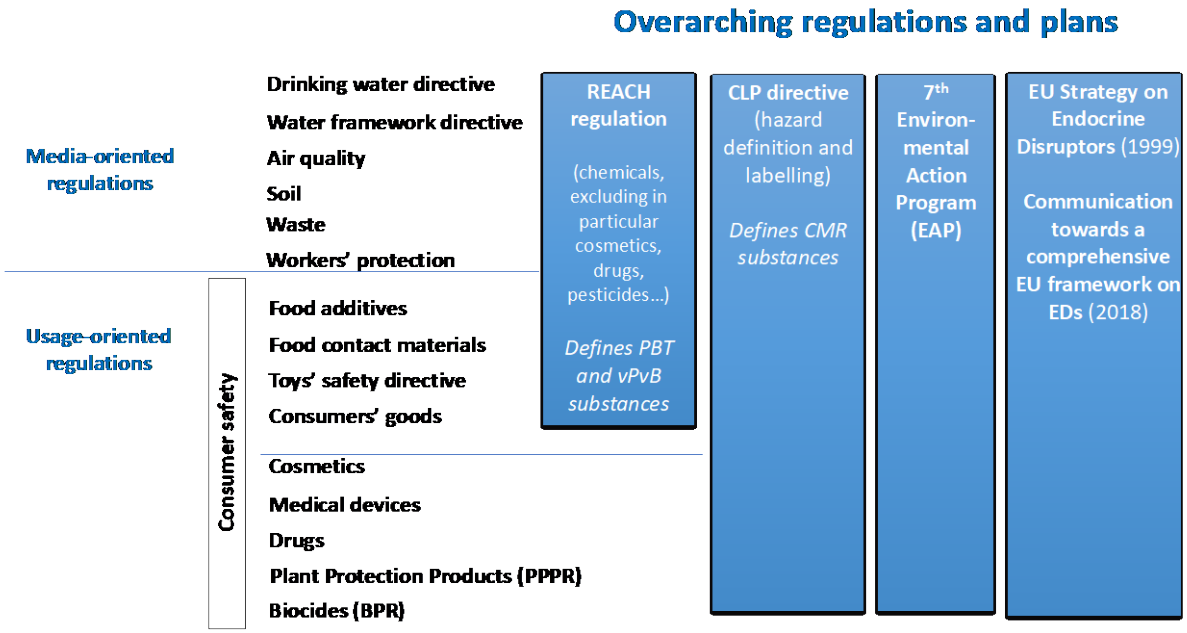
3 CURRENT REGULATION OF ENDOCRINE DISRUPTORS IN THE EU

KEY FINDINGS

- In principle, the regulation of hazardous substances requires five main components: (1) hazard definition, (2) validated tests; (3) guidance to explain how to apply the definition based on test results and scientific publications; (4) test requirements (steps 1-4 allow hazard identification); and (5) a management logic.
- A legal definition of EDs exists for the sector of biocides and plant protection products (pesticides) but not in other key sectors (REACH chemicals, cosmetics, food additives and food contact material, toys…).
- Even for biocides and plant protection products, the regulation lacks coherence, in that a definition and a management logic exist (zero exposure to EDs) but without tests covering the main ED modalities and endpoints being compulsory in application dossiers for product authorization, making identification of EDs very difficult in practice.
- Currently, only 13 REACH chemicals have been classified as EDs, in part due to limited information in the application dossiers. Two compounds on the list of substances of very high concern have been added to the REACH list of substances requiring authorization because of their endocrine-disrupting properties.
- For sectors other than plant protection products and biocides, although regulations in some cases required definitions to be put forward (e.g. for cosmetics), no definition ("identification criteria") has been proposed and generally no management logic specific to EDs exist. A partial exception is that of REACH regulation, which puts EDs on the same level of concern as carcinogenic, mutagenic substances and reprotoxicants, but without making ED testing compulsory in application dossiers for product authorization.
- Some compound- and sector-specific regulations for EDs also exist (e.g., ban of bisphenol A in food contact materials for children until 3 years), but given that they apply to compounds present in multiple sources and sectors, such provisions will only partially decrease exposure.
- Thus, despite the significant progress that REACH, the plant protection products and biocides regulations represent, neither the current regulatory framework nor its implementation, are sufficient to protect human health and the environment from the impact of EDs. Given the limitations for ED identification noted above, it is very unlikely that the aim of having all EDs recognized as substances of very high concern by 2020 will be achieved, as promised by the 7th Environment Action Programme.

A succinct overview of the sectors and regulations dealing with health and environmental hazards is provided Figure 14. These hazards in general, and EDs specifically, are mentioned in some of these regulations, be they media-oriented or use-oriented. Currently, they are considered in the regulations relative to pesticides (plant protection products and biocides, see 3.2 below), in REACH regulation (3.3), and (more succinctly) mentioned in the cosmetics regulation (3.4), all of which are presented below. We also describe regulations central for the protection of health and the environment or the management of chemicals in which EDs are not mentioned, such as the toys' safety directive (see 3.6 below) and the CLP (Classification, Labelling, Packaging) directive, an important regulation defining the main categories of hazards, including hazards for health and the environment, but not EDs (3.8). A summary of the current regulation is provided in Table 7, and in a simplified version in Table 1. For size limitation reasons, this review does not constitute an exhaustive presentation of the EU chemicals regulation.

Figure 14: EDs are expected to be present in different sectors; list of the main EU regulatory areas with relevance to endocrine disruption. Adapted from [7].



3.1 Overarching regulations

3.1.1 The 7th environment action programme

The EU policy on environment and health is framed in its Environment Action Programmes (EAPs). The 7th EAP (decision 1386/2013/EU[22]), encompassing the 2013-2020 period, recalls that:

> The Union has agreed to achieve, by 2020, the objective that chemicals are produced and used in ways that lead to the minimisation of significant adverse effects on human health and the environment[23].

And that:

> The Union has agreed to stimulate the transition to a green economy and to strive towards an absolute decoupling of economic growth and environmental degradation.

This programme states notably that:

> efforts need to be stepped up to ensure that, by 2020, all relevant substances of very high concern, including substances with endocrine-disrupting properties, are placed on the REACH candidate list. (Article 50)

It is also recalled that:

> Pursuant to Article 191(2) of the Treaty on the Functioning of the European Union (TFEU), Union policy on the environment aims at a high level of protection taking into account the diversity of situations in the various regions of the Union, and is based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should, as a priority, be rectified at source and that the polluter should pay.

[22] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013D1386&from=EN
[23] Decision No 1600/2002/EC; Johannesburg Plan of Implementation (WSSD 2002).

Note that the Precautionary principle is, in the EU framework, meant to be applied to environment, health, animal or plant health:

> Although the precautionary principle is not explicitly mentioned in the Treaty except in the environmental field, its scope is far wider and covers those specific circumstances where scientific evidence is insufficient, inconclusive or uncertain and there are indications through preliminary objective scientific evaluation that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the chosen level of protection.[24]

More specifically, legislation on the Circular Economy Package was introduced recently, with member states having 24 months to enact the law in their national equivalents. Notably, by 2030 all plastic packaging should be recyclable. The case of EDs within the circular economy has recently been addressed by the EU Parliament in its resolution (2018/2589(RSP) tabled in September 2018. The resolution raised the twin problems of EDs in recycled products and the need to consider ED in the design stage of the product.

3.1.2 1999 EU strategy on EDs

Historically, the first reference to EDs by the European Parliament dates back to 1998, with a resolution calling upon the European Commission to take action on the issue of EDs, aiming for an improvement of the legislative framework, reinforcement of research efforts and an increased effort to make information available to the public. This resolution was followed by a "Community strategy for EDs – a range of substances suspected of interfering with the hormone systems of humans and wildlife" in 1999[25]. The strategy listed short to long-term actions, as summarized elsewhere[26]:

Short-term actions (1-2 years) included:

- Establish a priority list of substances for further evaluation of their role in endocrine disruption including the identification of a) substances for priority testing b) substances addressed/regulated under existing Community legislation, c) gaps in knowledge d) specific cases of consumer use e.g. by vulnerable groups such as children
- Establish monitoring programmes to estimate exposure to and the effects of the substances on the ED priority list
- Collect, exchange, assess and provide information on EDs to the public

Medium-term actions (2-4 years):

- Identify and assess EDs: include harmonisation of the development and validation of new improved testing methods
- Research and development to provide greater understanding of the mechanisms of endocrine disruption, causal links between exposure to substances and adverse effects in humans and wildlife, investigation of risk assessment concepts, exposure assessment and the development of environmental monitoring tools

Long-term actions (4 years or more):

[24] European Commission, COM(2000)1 of 2 February 2000, see https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52000DC0001&from=EN
[25] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:51999DC0706
[26] http://ec.europa.eu/environment/chemicals/endocrine/documents/index_en.htm#SubThemes2

- Adapt and/or amend present EU legislative instruments which cover chemical as well as consumer, health and environmental protection to take account of ED effects

3.1.3 The 2018 Communication toward a comprehensive EU framework on EDs

In 2018, the EU Commission published a "Communication toward a comprehensive EU framework on EDs" [101] (sometimes referred to orally as the "2018 ED strategy"). This Communication states that:

> The implementation of the Community Strategy of 1999 has put the EU at the forefront in understanding and regulating these hazardous chemicals. But in order to further progress and maintain the expected high level of protection, it is important to ensure that the EU framework continues to coherently address endocrine disruptors across different areas.

The main aims to follow in this sector for the years to come are listed:

> The EU strategic approach on endocrine disruptors for the years to come should be based on the application of the precautionary principle and aim at:
>
> - minimising overall exposure of humans and the environment to endocrine disruptors, paying particular attention to exposures during important periods of development of an organism, such as foetal development and puberty;
> - accelerating the development of a thorough research basis for effective and forward-looking decision-making;
> - and promoting an active dialogue allowing all stakeholders to be heard and to work together.

Thus, the main concrete goal lies in the minimisation of overall exposure of humans and the environment to EDs.

To move in this direction, the communication acknowledges that

> The legislative measures constituting the EU legal framework regulating chemicals have been developed at different points in time and have, in certain cases, different objectives. This has resulted in different approaches to endocrine disruptors, depending on the sector being regulated, and has raised questions as to whether the EU legal framework regulating endocrine disruptors is sufficiently coherent.

(these different approaches to the regulation of EDs in different sectors are discussed below in 4.1.2 and 4.1.3).

Specifically, the need for a horizontal identification of EDs across sectors is acknowledged:

> Horizontal approach to the identification of endocrine disruptors: the Commission considers that there should be a coherent approach to the identification of endocrine disruptors across all relevant Union legislation, based on the broadly accepted definition of the World Health Organisation.

(see 4.2 below for a discussion).

Importantly, beyond the lack of homogeneous identification of EDs across sectors, the heterogeneous management of EDs in different sectors is also acknowledged:

> Regulatory consequences for endocrine disruptors: different regulatory approaches exist in different pieces of legislation for substances identified as endocrine disruptors.

The main actions planned in this regard consist in supporting scientific research, the organization of a yearly forum on EDs, the launch of a web portal on EDs, the support for the recognition of the definition

of EDs in the international system for classification of chemicals, and the launch of a "fitness check". However, no detailed plan regarding changes in the regulation are laid down to tackle this issue:

> Some stakeholders have argued that, in some areas, EU legislation does not provide adequate regulatory approaches to address endocrine disruptors effectively. This matter deserves further examination.

We discuss this issue in chapter 5. Comments on this Framework have also been provided by scientific societies including the Endocrine Society[27] and the European Society for Endocrinology[28]. Both societies underlined that the strategy described in the communication will fail to fully protect human health and the environment. Notably, the European Society of Endocrinology deplores the absence of concrete measures and time-points to achieve them.

3.2 The plant protection products (PPPR) and biocides (BPR) regulations

3.2.1 Management of plant protection products and biocides containing EDs

The management of plant protection products follows the logic that the plant protection products should not be authorized if they have endocrine disrupting properties. More specifically, the plant protection products regulation (1107/2009) states that:

> The residues of the plant protection products… (a) shall not have any harmful effects on human health, including that of vulnerable groups, or animal health, taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available, or on groundwater; (b) they shall not have any unacceptable effect on the environment. (article 4)

Annex II lists the Procedure and criteria for approval of active substances, safeners and synergists in plant protection products, specifically stating that these shall only be approved if they are not considered to have ED properties, unless the exposure of humans is negligible:

> An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not considered to have endocrine disrupting properties that may cause adverse effect in humans, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005. (Annex II, 3.6.5)

Note that a similar provision exists for plant protection products recognized as carcinogens (level of evidence 1A or 1B, that is, known or presumed carcinogens, annex II, 3.6.3), mutagens (1A and 1B) and toxic for reproduction (annex II, 3.6.4). Thus, the PPPR regulation follows a similar management logic for CMRs and substances with ED properties. However, unlike CMRs which had a legally valid definition in 2009, substances with ED properties did not, so this logic was not implemented at once. Article 3.6.5 (annex II) of the PPPR further requested a draft definition to be presented by the EU Commission by

[27] https://www.endocrine.org/news-room/2018/european-commission-communication-falls-short-of-protecting-public-from-edc-exposure

[28] ESE statement commenting on EC Communication from November 07: https://www.ese-hormones.org/media/1600/ese-statement-on-ec-com_final.pdf

December 2013. This was not done at this time, and a definition (the so-called "ED criteria", see 3.2.2) was eventually adopted and applied as of October 2018 for plant protection products. As yet (January 2019), to our knowledge, no plant protection product or biocide has been banned due to its ED properties[29]. Given the existence of a scientifically recognized definition of EDs in the World Health Organization 2002 report (and of earlier definitions internationally agreed upon by scientists), there is no scientific justification for the lack of definition of EDs between 2009 and 2018.

The BPR, or biocidal product regulation (528/2012), follows a logic similar to that laid down for biocides, i.e. that "active substances which…are considered as having endocrine-disrupting properties that may cause adverse effects in humans or which are identified in accordance with [REACH] regulation as having endocrine disrupting properties" shall not be approved (article 5). It may however be approved for an initial period not exceeding five years if "the risk to humans, animals or the environment from exposure to the active substance in a biocidal product, under realistic worst case conditions of use, is negligible, in particular where the product is used in closed systems or under other conditions which aim at excluding contact with humans and release into the environment" (article 5(2)). Identical provisions exist for active substances classified as CMRs (categories 1A or 1B), PBT or vPvB. A distinction with the plant protection products regulation relates to the replacement of the term "negligible exposure…" in the plant protection products (2009) regulation by the term "negligible risk…"[30] in the biocides (2012) regulation, although the context (exclusion of contact with humans and release into the environment) remains the same. The clause of authorization of active substances for which risk is negligible does not apply to biocidal products for use by the general public (Article 19(4)). The Commissions' interpretation [101], which seems a logical interpretation of the biocide law, is that quantitative risk assessment is not required for biocides containing EDs or CMRs and that a no exposure logic is to be applied, like for pesticides.

3.2.2 Definitions of EDs for plant protection products and biocides

The WHO-IPCS [9, 252] definition of ED served as the basis of the definition of substances with endocrine disrupting properties in the context of the 2009 EU Plant Protection Products Regulation (PPPR)[31], which rephrases the definition the following way:

- an active substance, safener or synergist shall be considered as having endocrine disrupting properties that may cause adverse effect in humans if [...] it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant to humans:
- it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;
- it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;
- the adverse effect is a consequence of the endocrine mode of action.

The comparison with the WHO definition notably shows:

[29] Triclosan has been banned as a biocide, due to its toxicity for aquatic life.

[30] *Risk* is defined as the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.

[31] Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. *Link*.

- the reference to active substances, safeners or synergist, which is specific to the area of plant protection products and biocides;
- the absence of reference to effects in populations or subpopulations, referred to in the WHO definition;
- the use of the expression "mode of action" in the EU ED criteria for plant protection products and biocides.

We discuss the relevance of these modifications in 4.2.2

3.2.3 Identification of EDs for plant protection products and biocides

The Commission regulations appending the annex II of the PPPR and BPR [253, 254], or so-called "ED criteria", additionally specify that:

- A *weight of evidence* (WoE[32]) approach should be used for the assessment of the available data;
- All available relevant scientific data (*in vivo* studies or adequately validated alternative test systems predictive of adverse effects in humans or animals; as well as *in vivo*, *in vitro*, or, if applicable, *in silico* studies informing about endocrine modes of action) must be considered in applying this WoE approach: (a) scientific data generated in accordance with internationally agreed study protocols, in particular those listed in the Commission Communications in the framework of setting out the data requirements for active substances and plant protection products, in accordance with this Regulation; (b) other scientific data selected applying a systematic review methodology […];
- The application of the WoE approach should consider: both negative and positive results; the relevance of study designs; the quality and consistency of the data […] within and between studies of a similar design and across different species"; the route of exposure, toxicokinetic and metabolism studies;
- "The link between the adverse effect(s) and the endocrine mode of action shall be established based on biological plausibility";
- "Adverse effects that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor".

It can be noted that, in accordance with the PPPR and BPR, two definitions are actually provided, one for *substances with endocrine disrupting properties that may cause adverse effects in humans* and one for *substances with endocrine disrupting properties that may cause adverse effects on non-target organisms*.

No further categories of substances with endocrine disrupting properties (e.g., distinguishing according to the level of evidence) are defined in the context of the EU regulation.

Further, a guidance document from ECHA and EFSA [255] stipulates how to perform hazard identification for endocrine-disrupting properties in the context of the PPPR and BPR on the basis of these ED criteria and of test results from the authorization dossiers. Specifically, this guidance document "describes how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action

32 "Weight of evidence assessment is defined … as a process in which evidence is integrated to determine the relative support for possible answers to a question. [The weight of evidence assessment comprises] three basic steps: (1) assembling the evidence into lines of evidence of similar type, (2) weighing the evidence, (3) integrating the evidence." (EFSA guidance on weight of evidence, EFSA Journal, 2017, https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4971).

(MoA) analysis, and apply a weight of evidence (WoE) approach, in order to establish whether the ED criteria are fulfilled." [255].

We discuss the ED criteria in 4.2.1 and the ECHA-EFSA guidance document in 4.3.1.

3.2.4 Test requirements to identify plant protection products and biocides with ED properties

The test requirements regarding plant protection products and biocides are listed in regulations 283 and 284/2013 (EU) for plant protection products and 528/2012 for biocides and reiterated in the Guidance document [255]. The requirements are summarized in Table 5. For active substances used in plant protection products, there are explicit test requirements relative to the identification of oestrogenicity, anti-androgenicity, thyroid disruption. The requirements for the identification of compounds toxic for reproduction additionally requires tests on anogenital distance and nipple retention, which are also sensitive to anti-androgenic substances. Overall, many of these tests have a low sensitivity and sometimes high variability [250, 251]. No *in vitro* screening of the product by available OECD validated tests with nuclear receptors is required if an *in vivo* test of oestrogenicity is performed. If this *in vivo* test is not performed, data for oestrogen receptor activity can come from the US ToxCast ER models.

Table 5: Tests required to identify EDs in various sectors of the EU regulation.

Area	Regulation	Test requirement
Plant protection products	Active substances: 283/2013 (EU) and 2013/C 95/01; Plant protection products: 284/2013 (EU)	For active substances: *Oestrogenicity*: ToxCast ER models *or* uterotrophic assay (OECD TG 440) *Anti-androgenicity*: Hershberger assay (OECD TG 441) *Thyroid disruption*: OCSPP Guideline 890.1450: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal female rats' assay. *Steroidogenesis*: H295R assay (OECD TG 456) No mention to ED nor ED tests required specifically in regulation 284/2013.
Biocides	528/2012 (BPR, annex II)	Testing requirements for EDs are those requested by REACH regulation. However, the requirements specific to EDs in REACH are very limited (see below).
Cosmetics	1223/2009 (EC)	No identification of ED required.
REACH chemicals	1907/2006 (EC); 440/2008 (EC)	Extended One-Generation Reproductive Toxicity Study (OECD 421 or 422) with the extension of cohort 1B to include the F2 generation if 1) significant exposure and 2) there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches.
Food additives	1333/2008/, 234/2011/EU, EFSA (2009)[33]	No specific test for ED identification required.
Food contact materials	1935/2004/EC	No specific test for ED identification required.
Consumer goods	1999/44/EC	No specific test for ED identification required.
Drinking water	98/83/EC	No specific test for ED identification required.
Toys	2009/48	No specific test for ED identification required.
Workers' protection	89/391/EEC	No specific test for ED identification required.
Medical devices	2017/745/EU	Same requirements as in REACH regulation (see above)

For biocides, the requirement regarding the testing of EDs corresponds to that laid down in REACH regulation, which turns out to be very limited (see 3.3.4).

[33] https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2009.1188

3.3 REACH chemicals regulation

3.3.1 General principles and aims of REACH regulation

REACH regulation (2006R1907 (EC)) deals with the registration, evaluation, authorization and restriction of chemicals in the EU. This regulation does not deal with plant protection products, biocides, cosmetics, drugs and certain other sectors, that are regulated distinctly.

REACH regulation aims at achieving that "by 2020, chemicals are produced and used in ways that lead to the minimization of significant adverse effects on human health and the environment" (recital 4); it aims "to ensure the good functioning of the internal market while assuring that the risks from substances of very high concern are properly controlled and that these substances are progressively replaced by suitable alternative substances or technologies where these are economically and technically viable" (article 55).

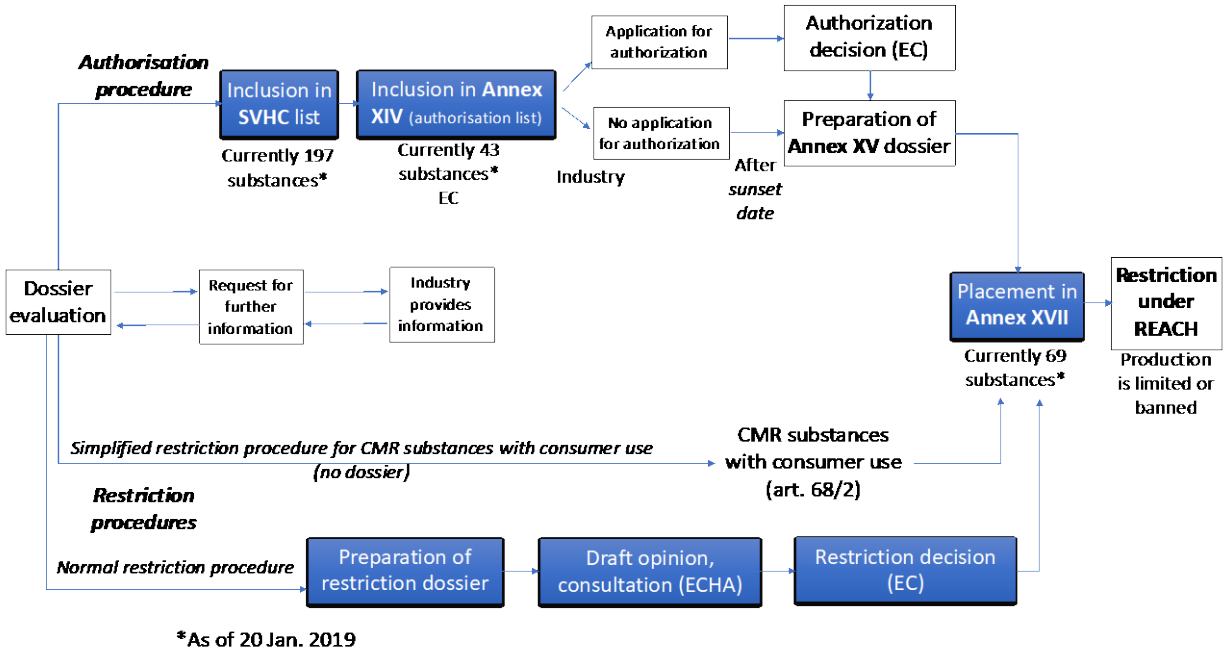
3.3.2 Management of EDs under REACH regulation

Substances with endocrine disrupting properties may be included in the annex XIV (article 57 or REACH regulation), together with carcinogens, mutagens, substances toxic for reproduction substances with persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative properties (vPvB), if they are shown to be of equivalent concern (Figure 15). This annex XIV of REACH contains substances requiring authorization. In practice, the placement of a compound in annex XIV means that the EU Commission shall specifically grant an authorization for the marketing of the substance – this shall happen "if the risk to human health or the environment from the use of a substance arising from the intrinsic properties specified in Annex XIV is adequately controlled". If the authorization cannot be granted under this logic, then "an authorization may only be granted if it is shown that socio-economic benefits outweigh the risk to human health or the environment arising from the use of the substance and if there are no suitable alternative substances or technologies." (commonly referred to as the "socio-economic route") (Article 60 of REACH regulation). In no way does the placement on the authorization list constitute a ban of the substance or a guarantee that human exposure will cease.

Many years can pass between the substance being placed on this list and any restriction of use being officially decided by the Commission. This placement in annex XIV may imply limitations of use, such as a presence of the compound in the manufactured product that shall not exceed 0.1% of the product weight; this may happen after some duration, if no authorization is eventually granted. As of 14 Jan 2019, 43 substances had been placed in annex XIV of REACH, two of which are recognized EDs.

Another route that can lead to limitations of use of a compound is the *restriction* route (Figure 15). A simplified restriction procedure can be taken for articles that meet the criteria for CMR substances and that could be used by consumers, for which placement in annex XVII (restricting manufacture, marketing and use) is planned (article 68.2). While articles that could be used by consumers are those representing the highest likelihood of human exposure, this article does not mention EDs.

Figure 15: Schematic view of the authorization and restriction procedures of REACH, possibly leading to the restriction of marketing of hazardous substances.



One can note that, in its article 57 f), REACH regulation actually does not exactly refer to EDs the way CMR substances are mentioned. The exact phrasing is that "substances…having endocrine disrupting properties… for which there is evidence of probable serious effects to human health or the environment which give rise to an equivalent concern to those of other substances listed in points (a) to (e) and which are identified on a case by case basis…". Regarding this specific point, the regulation called for a review and possible revision of the law by the European Commission so that EDs are exactly handled as CMR , PBT and vPvB substances (article 138.7). This review was due in June 2013, and was published in 2016[34]. It concluded that, since it was not possible to assume that all EDs acted without a threshold effect, no change in REACH regulation regarding EDs was required. More specifically, the current practice is that the applicant for authorisation of an ED shall demonstrate in their application file that a threshold for the health or environmental effect exists. If not, or if this demonstration is not accepted by ECHA, then the candidate substance will be subject to authorization via the so-called "socio-economic route"[35].

3.3.3 Definition and identification of EDs under REACH regulation

In spite of the provisions regarding the management of substances with ED properties within REACH, EDs are not defined as part of REACH or any related regulation. Notwithstanding this lack of definition, REACH regulation allows Member States to submit dossiers to put substances on a candidate list of substances to be subject to authorisation. So far, 13 chemicals (including bisphenol A, DEHP, nonylphenol) have been put on the list of substances of very high concern (SVHC) because of their endocrine-disrupting properties in the context of REACH regulation (Table 6). This is likely to represent a small proportion of all marketed suspected EDs, and also of certain EDs. So far two have been put in REACH Annex XIV of substances requiring authorization, and an additional four phthalates may enter this annex in 2019 due to their endocrine-disrupting properties (DEHP, DBP, BBP and DIBP).

[34] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52016DC0814&from=en

[35] "…Consequently, Article 60(3) of REACH will continue to be applicable to those EDs for which it is not possible to determine a threshold. It remains the responsibility of applicants for authorization to demonstrate that a threshold exists and to determine that threshold in accordance with Annex I to REACH. Even though this might be particularly difficult for EDs, it cannot be excluded on the basis of current knowledge that it will be possible. It is up to RAC to assess the validity of the assessment and ultimately decide on the possible existence or not of this threshold. Furthermore, as for other substances, RAC may on a case- by-case basis set reference DNELs, or reference dose-response curves, which industry can use when applying for authorization. Therefore, as under REACH as it stands today only the "Socio-Economic Route" can be used when a threshold cannot be determined…"

Table 6: List of legally recognized EDs in the EU. This corresponds to the substances added to the REACH list of substances of very high concern because of their endocrine-disrupting properties.

Substance acronym and name	CAS number	Date of Inclusion	Reason for inclusion
3-BC - 1,7,7-trimethyl-3-(phenylmethylene)bicyclo[2.2.1]heptan-2-one. 3-benzylidene camphor	15087-24-8	2019	ED properties – environment
DCHP - Dicyclohexyl phthalate	84-61-7	2018	Toxic for reproduction (Article 57c) ED properties - human health
RP-HP - Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear		2018	ED properties – environment
BPA - 4,4'-isopropylidenediphenol Bisphenol A	80-05-7	2017	Toxic for reproduction (Article 57c) ED properties - environment. ED properties - human health
4-HP - 4-heptylphenol	-	2017	ED properties – environment
PTAP - p-(1,1-dimethylpropyl)phenol	80-46-6	2017	ED properties – environment
4-Nonylphenol		2013	ED properties – environment
4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated		2012	ED properties – environment
4-(1,1,3,3-tetramethylbutyl)phenol	140-66-9	2011	ED properties – environment
DIBP - Diisobutyl phthalate	84-69-5	2010	Toxic for reproduction ED properties - human health
BBP - Benzyl butyl phthalate	85-68-7	2008	Toxic for reproduction ED properties - human health
DEHP - Bis (2-ethylhexyl)phthalate	117-81-7 -	2008	Toxic for reproduction ED properties - environment ED properties - human health
DBP - Dibutyl phthalate	84-74-2 -	2008	Toxic for reproduction ED properties - human health

Source: ECHA[36]

3.3.4 Test requirements to identify which REACH chemicals are EDs

When it comes to test requirements, however, REACH and the related regulations appear very limited (see Table 5). Specifically, REACH regulation states that

> Information on any other adverse effects on the environment shall be included where available, such as environmental fate (exposure), photochemical ozone creation potential, ozone depletion potential, endocrine-disrupting potential and/or global warming potential. (section II, 12.6)

But this seems restricted to "available" information (not an information that the applicant should generate if it is not already available).

Thus, although the principles laid down in REACH regulation call for identification of EDs, the current regulation does not compel application dossiers for products authorization about existing or new chemicals or products to be put on the EU market to contain enough information to ensure that agencies and other relevant bodies can identify if the substance is an ED or not. Only if a substance has been on the market for some time and thoroughly studied by academic research (as is the case of bisphenol A or DEHP for example), can it be expected to have generated enough information to decide if the substance has endocrine-disrupting properties.

[36] https://echa.europa.eu/candidate-list-table

Another illustration of the fact that most information relevant for the identification of EDs is not regulatorily requested or available in REACH dossiers was provided through an effort of the French environmental health agency ANSES to evaluate 15 REACH chemicals, as part of the French Strategy on Endocrine Disruptors (SNPE1): ANSES evaluated the dossiers of 15 substances of concern. For 10 of them (two thirds), it was not possible to conclude if the compound had endocrine properties or not, showing that the majority of dossiers for substances with some a priori concern do not contain the relevant information.

It should be noted that, at least for substances already on the market, the fact that a substance cannot be classified in terms of ED properties will generally have no immediate consequence regarding the marketing of the substance, which will stay on the market. It is our understanding that, if for some reason, the Member State in charge of the evaluation of the substance has reason to believe that the substance might be an ED, then additional information may be requested to the industry marketing the substance. This procedure, according to the kind of test required may take some time, and whilst awaiting the results the product will remain on the market. Thus, it seems that, in the case an applicant has some doubt that a substance he wishes to continue selling might be an ED, there is little incentive or requirement for him to perform all the required tests that could lead to the identification of the substance as an ED, and little legal risk, if any, in not doing these tests.

3.3.5 Conclusion regarding REACH regulation

REACH regulation provides an overall framework for the regulation of chemicals in many areas in the EU, allowed recognition of the hazards incurred by many substances, and as such represents a clear progress towards a safe and sustainable use of chemicals.

REACH regulation aims at minimizing significant adverse health effects on human health and the environment, recognizes EDs as substances of very high concern and, as such, puts them on the same level of concern as carcinogens, mutagens and reprotoxicants. However, beyond this (not very specific and explicit) management logic, REACH regulation does not rely on any definition of EDs; it does not recognize criteria about EDs nor is there any guidance document explicating how to identify EDs. The test requirements planned in relation to REACH regulation are very limited, not providing enough evidence allowing to conclude if a chemical is an ED or not. Given that ECHA, the Commission and Member States managed to identify some substances as EDs even without a legal definition, the regulatory efforts regarding REACH should focus on the test requirements in application dossiers and on the management of substances identified as EDs.

Given the limited information present in dossiers, ECHA and the national evaluation agencies should be complimented for having managed to include compounds on the list of substances of very high concern because of their endocrine-disrupting properties. However, so far, only two compounds present on the list of substances of very high concern have been added to REACH Annex XIV authorization list because of their endocrine-disrupting properties. Even assuming that this figure increases to 6 in 2019, as can be expected, this would correspond to a ratio of less than 1 out of 10,000 REACH chemicals subject to authorization because of its endocrine-disrupting properties. This figure suggests that, in spite of the progress it represents, when it comes to the protection of health and the environment from the impact of EDs, REACH regulation is currently doing too little too slowly. At this stage, it seems unlikely that the aim of the 7th Environment Action Programme to have all EDs recognized as substances of very high concern by 2020 will be achieved.

3.4 Regulation of EDs in cosmetics

3.4.1 General principles of the cosmetics regulation

The cosmetic regulation (1223/2009 (EC)) aims at ensuring a high level of protection of human health (recital 4) and states that "cosmetics should be safe under normal or reasonably foreseeable conditions of use. In particular, a risk-benefit analysis should not justify a risk to human health." (recital 9; a similar provision exists in article 3). The regulation also requires that "the responsible person shall, prior to placing a cosmetic product on the market, ensure that the cosmetic product has undergone a safety assessment … and that a cosmetic product safety report is set up…" (article 10). It is also recalled that "action by the Commission and Member States relating to the protection of human health should be based on the precautionary principle" (recital 36).

This regulation includes a list of substances prohibited in cosmetic products (annex II), a list of colorants (annex IV), preservatives (annex V) and UV filters (annex VI) allowed in cosmetics.

The cosmetic regulation also mentions (recital 5) that the *environmental* concerns of substances present in cosmetics on the environment are considered through the application of REACH regulation (see 3.3 above).

3.4.2 Management of EDs present in cosmetics

The cosmetic regulation further states that "Given the hazardous properties of substances classified as carcinogenic, mutagenic or toxic for reproduction (CMR), category 1A, 1B and 2… their use in cosmetic products should be prohibited. However, as a hazardous property of a substance does not necessarily always entail a risk, there should be a possibility to allow the use of substances classified as CMR 2 substances where, in view of exposure and concentration, they have been found safe for use in cosmetic products by the SCCS…" (recital 32). Coherently, article 15 ("Substances classified as CMR substances") mentions that "The use in cosmetic products of substances classified as CMR substances of category 1A or 1B… shall be prohibited" (15.2, with some derogatory provisions for CMR substances complying with the food safety requirements for which there are no suitable alternative substances available and that have been evaluated and found safe by the SCCS for use in cosmetic products...). Article 15.1 similarly prohibits the use of substances classified as CMR substances of category 2, with a possible derogation if the SCCS finds the substance safe for use in cosmetic products.

The same article refers to EDs, stating that "When Community or internationally agreed criteria for identifying substances with endocrine-disrupting properties are available, or at the latest on 11 January 2015, the Commission shall review this Regulation with regard to substances with endocrine-disrupting properties" (article 15.4). Consequently, there is no generic provision stating how EDs present in cosmetics should be treated, inferring that in practice they are handled on a compound-by-compound basis, unlike chemicals of specific concerns such as those with CMR properties.

Currently, as examples of suspected EDs, the list of authorized preservatives[37] includes parabens with a linear chain of 1 to 4 carbon atoms (while other parabens have been banned previously) and triclosan. Triclosan is authorized with a maximum concentration of 0.3%.

[37] http://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20V_v2.pdf

3.5 Other sectors in which the regulation refers to EDs

3.5.1 Water

The Council Directive on the quality of water intended for human consumption (98/83/EC) dates from 1998. It states that "Whereas there is at present insufficient evidence on which to base parametric values for endocrine-disrupting chemicals at Community level, yet there is increasing concern regarding the potential impact on humans and wildlife of the effects of substances harmful to health."

Drinking water standards underwent a "REFIT" procedure in 2015 and an impact assessment was presented to the EU parliament in February 2018. It proposed an updated list of parameters to be monitored and regulated, including two perfluorinated compounds (PFOS and PFOA, with suggested limit concentrations in drinking water of 0.4 µg/l and 4 µg/l, respectively), the sum of PFAS and three compounds included because of their endocrine-disrupting properties: bisphenol A, nonylphenol and beta-oestradiol. It was also recommended to lower the total authorized concentration for lead and chromium.

As concerns materials that come into contact with drinking water (pipes, joints etc.), technical standards are currently being developed within the Construction Product Regulations (No 305/2011), with limits for certain EDs (bisphenol A and PFASs).

3.5.2 Medical devices regulation

The medical devices regulation[38] (2017/745 (EU)) allows the presence of CMRs and EDs in the parts of the medical devices that come in contact with the body or with body fluids in a proportion above 0.1% of the weight only upon certain conditions, such as justification why substation by another less hazardous substance would be inappropriate (article 10.4). Specific guidelines regarding the use of phthalates are to be prepared by the Commission scientific committees.

The identification of EDs in medical devices refers to the ED criteria specified as part of the biocidal products regulation (528/2012), with the test requirements related to REACH regulation. As already discussed (see 3.3.4), these are too limited to allow proper identification of EDs.

3.6 Sectors in which the regulation does not explicitly refer to EDs

Many sectors of the EU regulation, including regulations of substances for which human exposure is likely or very likely, do not include any specific provisions regarding EDs. Among several relevant areas, we briefly discuss below the specific cases of the directives on the safety of toys (2009/48 (EC)), on workers' protection and on food contact materials (1935/2004 (EC)).

3.6.1 The toys' safety directive

As stated in the Commission ED framework published in 2018 [101], legislation "on food contact materials, cosmetics, toys or protecting workers at the workplace, does not contain specific provisions for endocrine disruptors. However, substances with endocrine disrupting properties are subject to case-by-case regulatory action on the basis of the general requirements of the legislation."

The toys directive (2009/48 (EC) mentions (Article 10.2) that "Toys, including the chemicals they contain, shall not jeopardise the safety or health of users or third parties when they are used as intended or in a foreseeable way, bearing in mind the behaviour of children."

[38] https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en

Article 11(2) deals with labels and the need to "draw the attention of users (..) to the inherent hazards and risks of harm involved in using the toys, and to the ways of avoiding such hazards and risks."

The Annex II (chemical properties) of the toys safety directive lists provisions for CMRs of category 1A, 1B or 2, stating that they "shall not be used in toys, in components of toys or in micro-structurally distinct parts of toys". The generic category of EDs is not restricted.

Limit values for chemicals used in toys for children under 36 months or in toys intended to be placed in the mouth are specified (Annex C); the list includes EDs such as bisphenol A (migration limit of 0.1 mg/l).

The toy directive also refers to the Restriction of Hazardous Substances (ROHS) directive (2011/65/EU), which as of 2019 will add four ED phthalates at concentrations of up to 1000 ppm to the list: BBP, DEHP, DIBP, and DBP. The list currently puts restrictions on lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyls (PBB), PBDEs (authorized below 1000 ppm). Note that PBDEs are known EDs [188-190]. Other EDs such as PFOS are regulated in the toy directive with reference to the POPs regulation (EC) (850/2004).

3.6.2 Workers' protection regulations

Certain work environments are associated with higher exposures to toxic chemicals including EDs, e.g. hairdressing and nail bar workers, those working in the cleaning sector, and in industries producing pharmaceutics, plant protection products and biocides. Note that many working in these sectors will be women of reproductive age.

The lack of consideration of EDs in general in the 1998 workers' regulation has been recognized in the 2018 Commission ED framework [101]. Note that there is a specific directive on the protection of workers from carcinogens and mutagens (2004/37/EC).

3.6.3 Food and food contact materials

The food regulation mentions that "The Community has chosen a high level of health protection as appropriate in the development of food law" (178/2002)[39]. This food directive refers to the precautionary principle (article 7). It also mentions that "…where there are reasonable grounds to suspect that a food or feed may present… a risk for human or animal health, then, depending on the nature, seriousness and extent of that risk, public authorities shall take appropriate steps to inform the general public of the nature of the risk to health, identifying to the fullest extent possible the food or feed, or type of food or feed, the risk that it may present, and the measures which are taken or about to be taken to prevent, reduce or eliminate that risk." (article 10).

In addition, there is a specific directive on food packaging (EC, 1935/2004), aiming to ensure the effective functioning of the internal market, and provide the basis for securing a high level of protection of human health and the interests of consumers. Its principles are that "any material or article intended to come into contact directly or indirectly with food must be sufficiently inert to preclude substances from being transferred to food in quantities large enough to endanger human health or to bring about an unacceptable change in the composition of the food or a deterioration in its organoleptic properties". This regulation does not identify any specific type of health hazard that requires specific consideration.

[39] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002R0178&from=FR

Table 7: Current status of the regulatory provisions defining EDs in various regulatory areas, or allowing the identification, and existence of explicit management logics. See also Table 1 for a simplified version.

	Steps required to manage health risks incurred by EDs			
Sector	**Definition of EDs**	**Identification tools**	**ED test requirements***	**Risk management logic of EDs as a whole**
Plant protection products	Existing definition	Existing guidance document	Limited	**Not authorized**, unless exposure is negligible.
Biocides	Existing definition	Existing guidance document	Very limited (requirements of REACH regulation)	**Not authorized** in biocidal products for the general public. Not authorized unless risk is negligible, in particular…under conditions which aim at excluding contact with humans and release into the environment for the other biocides.
REACH chemicals	**No legally vali definition**	**No guidance document on identification**	Very limited	**Recognized EDs can be put on "authorization list"** (Annex XIV) unless threshold can be demonstrated. Otherwise: "authorized dose" logic.
Cosmetics			**None**	**No generic management logic for EDs** (*compound by compound* approach)
Food additives				
Food contact material				
Drinking water				
Toys				
Workers' regulations				
Medical devices	Refers to the ED definition used for biocides		Very limited (requirements of REACH regulation)	**Limited to a proportion of 0.1%** in weight in parts of the device in contact with the body or body fluids.

*Requirement of test allowing to identify EDs. Conditions relative to the identification of a specific compound that is an ED or a suspected ED are not mentioned here.

Moreover, the commission regulation 10/2011[40] deals specifically with plastic materials and articles intended to come into contact with food. It stipulates that "monomers, other starting substances and additives should be risk assessed and authorised before their use in the manufacture of plastic materials and articles." This regulation precludes the use of CMR substances without authorization[41]. It does not mention EDs and therefore does not provide specific provision to protect human health from the hazard class of EDs present in plastics used as food contact materials. See section 2.2, for publications and data bases on EDs in food contact materials.

[40] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R0010&from=FR

[41] Specifically, "…a maximum level of 0,01 mg/kg in food should be established for the migration of a non-authorized substance through a functional barrier. Substances that are mutagenic, carcinogenic or toxic to reproduction should not be used in food contact materials or articles without previous authorization and should therefore not be covered by the functional barrier concept." (regulation 10/2011).

3.6.4 Food additives

The food additives regulation (1333/2008/EC) mentions that "Food additives must be safe when used, there must be a technological need for their use, and their use must not mislead the consumer and must be of benefit to the consumer." It also requires decisions regarding food additives to be based on the precautionary principle. The test requirements are laid down in EFSA scientific opinions relative to food additives[42], enzymes and flavours, which do not require application dossiers to contain any test specifically relevant to EDs.

3.7 Piecewise regulation of specific EDs

3.7.1 "Legacy" persistent chemicals suspected to be EDs (POPs)

Although this ban took place before the birth of the ED concept, one should mention the ban on the production and sale of various persistent substances considered by the scientific community to be possible, likely or very likely EDs, as part of the international Stockholm convention on Persistent Organic Pollutants (POP), ratified by the European Community in 2004. This includes a ban of the production and use of DDT, PCBs, chlordecone. A polybrominated flame retardant (PBDE) (commercial mixture, c-deca-BDE) is also restricted. The Stockholm convention proposed a ban on production of octa-BDE and that of penta-BDE[43], the bans becoming effective in the EU in 2004 and 1997 respectively. However, the deca-BDE can break down into the banned penta-BDE and octa-BDE forms, explaining the persistence of PBDEs in the environment and in the body of most EU citizens [256].

3.7.2 Bisphenol A

In 2011, following a 2010 decision from the French parliament that banned polycarbonate, a polymer made out of bisphenol A from baby bottles in France, a similar decision has been taken at the scale of the EU (regulation 321/2011). Bisphenol A has also been banned from food containers for infants and young children. Regarding the general population, a migration limit of bisphenol A from varnishes or coatings applied to materials and articles onto food shall not exceed 0.05 mg of bisphenol A per kg of food (Commission regulation 2018/213).

As of 2020, a maximum concentration of bisphenol A of 0.02% by weight shall be authorized in thermal papers in the EU, to limit the risk in people handling thermal paper receipts[44]. In toys, where EDs are not subject to specific restrictions, a migration limit of 0.1 mg/l has been set for bisphenol A. In 2017, bisphenol A has been recognized as a substance of very high concern (SVHC) for its endocrine disrupting properties by ECHA. It has not (yet) been added on REACH list of substances subject to authorization (annex XIV).

3.7.3 Triclosan

Triclosan use cannot be used in the manufacture of plastics intended to come in contact with food. In cosmetics, it is authorized up to a concentration of 0.3% in soaps and toothpastes, and 0.2% in mouthwashes.

[42] https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2009.1188
[43] http://chm.pops.int/Implementation/NIPs/Guidance/GuidancefortheinventoryofPBDEs/tabid/3171/Default.aspx
[44] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32016R2235

3.7.4 Phthalates, including DEHP

Four phthalates (BBP, DEHP, DIBP and DBP) have been recognized as EDs under REACH and they have been added in REACH annex XIV. The use of DEHP, DBP and BBP is limited in plasticized materials used in toys and childcare articles; this limitation is expected to be extended to DIBP, and to consumer products in general.

3.7.5 Are piecewise regulations of specific EDs efficient? The example of bisphenol A

Taking the example of the case of bisphenol A, exposure is expected to start long before birth, via the contamination of the foetus by bisphenol A contained in the diet and possibly cosmetics of the mother, given that bisphenol A readily passes the placental barrier. It is our perception that certain regulations (e.g., reduction of early-life exposure to endocrine disruptors, in the case of the bisphenol A ban from baby bottles and food containers intended for infants and young children) can be seen as a first regulatory step for minimizing exposure of susceptible populations. However, given that bisphenol A crosses the placenta and the authorization of bisphenol A in food and consumer goods used by pregnant women, in utero exposure is expected. From a public health perspective, given the reported effects of bisphenol A at very low doses, trying to avoid bisphenol A exposure in the first years of life but not in the prenatal period does not constitute a coherent and sufficient approach. We further discuss the gaps in the current regulation in 4.1.

3.8 The Classification Labelling and Packaging (CLP) directive

Before turning to examples of actions on EDs in some Member States, we present the important CLP directive. The CLP directive (regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures) aims at ensuring "a high level of protection of human health and the environment as well as the free movement of chemical substances, mixtures and certain specific articles, while enhancing competitiveness and innovation" (recital 1); its objective is to define the main classes of hazards, including physical hazards, health hazards, hazards to the environment, so that these hazards can be properly identified and communicated. The CLP directive provides definitions for carcinogenic, mutagenic substances and substances toxic for reproduction (see Table 8), but not for EDs.

The Directive does not apply to sectors such as cosmetics, animal nutrition, animal or human drugs, medical devices, food or feeding stuffs for humans or animals. It calls on reliance on the Globally Harmonised System (GHS) of classification and criteria developed internationally in the context of the United Nations. The responsibility for the identification of hazards of substances and mixtures and for deciding on their classification lies mainly with manufacturers, importers and downstream users of these substances or mixtures (…) (Recital 16).

CLP mentions that the resources of the authorities should be focused on substances of the highest concern with regard to health and the environment, and explicitly lists substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity (categories 1A, 1B or 2), for respiratory sensitisation or in respect of other effects on a case by case basis (recital 52 and article 36). According to international developments, the classification and labelling of persistent, bioaccumulative and toxic (PBT) substances and very persistent very bio-accumulative (vPvB) substances should also be included in the directive (recital 56), but in no instance are EDs mentioned.

3.9 Examples from specific Member States

3.9.1 Denmark

The Danish population and government first became aware of the problems of ED when the first studies on the temporal decline in sperm concentration in men from the EU and USA, authored by Danish researchers in the Department led by Professor Niels-Erik Skakkebaek, were published in 1992 [257, 258]. Comprehensive studies later documented an increase in testis cancer in the Danish population; a high frequency of sub-optimal semen quality in young men and of malformations of the male reproductive organs (cryptorchidism, hypospadias) [259]. Since then the Danish government, through its Environmental Protection Agency has been very active on EDs, increasing the knowledge base on EDs, setting up screening tests and enforcing regulations. It maintains a list of potential EDs, which currently lists 432 chemicals[45]. The list categorises them according to their level of evidence. All chemicals classed within category 1 (which includes many substances that are already prohibited or restricted at the EU level) are included in the Danish Government's list of undesirable substances (in Danish).

3.9.1 France

Public concern led France to be one of the first countries, after Canada, to ban bisphenol A in babies' bottles in 2010. As of 2015, it also banned bisphenol A from all food contact materials, first in those aimed at children until the age of three years (a similar decision has now been taken at the EU level) and then in all food contact materials, irrespective of the user's age, and thus including women of reproductive age.

The 2019 project of French national strategy on EDs (SNPE2[46]) highlights several actions to be enacted over the next four years with a view to protecting the population and the environment by reducing exposure to EDs. Targets include publishing a list of potential EDs by 2021 (classified by level of proof and/or need for further investigation), better informing the population, in particular through the labelling of consumer goods, improving knowledge on PE effects on wildlife and reducing environmental contamination by EDs.

3.9.2 Sweden

In 2015, the Swedish government renewed its four year plan for a "Non-toxic environment". This plan, elaborated in collaboration with the Swedish Chemicals agency, refers specifically to reducing chemical risks in everyday life and has a focus on reproductive and child health, notably in the pre-school environment. There is also an action plan for highly fluorinated compounds, in which fire-fighting products are given high priority. As of January 2019, all companies (above a certain yearly turnover) based in Sweden have to detail information on perfluorinated substances in their notifications to the national registry and to provide information (by end 2020) on quantities produced or sold. The plan makes specific mention of the need to develop legislation for EDs within the EU legal framework.

[45] https://eng.mst.dk/chemicals/chemicals-in-products/endocrine-disruptors/the-eu-list-of-potential-endocrine-disruptors/
[46] http://www.consultations-publiques.developpement-durable.gouv.fr/strategie-nationale-sur-les-perturbateurs-a1916.html (link available until Feb. 8, 2019)

Table 8: List of the main hazards legally recognized in the EU regulation.

Type of hazard	Hazard definition and regulation	Management logic
Physical hazards		
Various categories (e.g., explosives), not detailed*	Not detailed here. (EC No 1272/2008)	
Health hazards		
Radioactivity	Not detailed here (96/29/Euratom, (EC))	
Acute toxicity	Acute toxicity means those adverse effects occurring following oral or dermal administration of a single dose of a substance or a mixture, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours. (1272/2008)	
Carcinogens	A substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. Category 1A: known to have carcinogenic potential for humans, classification is largely based on human evidence; Category 1B: presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. Category 2: Suspected human carcinogens. ((EC) No 1272/2008)	Banned from plant protection products, biocides (categories 1A, 1B), cosmetics, toys (levels 1A, 1B, 2). Subject to authorization for REACH chemicals, leading to specific bans. Specific regulation for carcinogens and mutagens in the occupational setting.
Germ cell mutagenicity	A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term 'mutagenic' and 'mutagen' will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms. *Category 1:* Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans. (categories 1A and 1B are defined). *Category 2:* Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.	
Reproductive toxicity	Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. *Category 1A (resp. B, C):* Known (presumed, suspected) human reprotoxicant. ((EC) No 1272/2008)	
Specific target organ toxicity (STOT) – *single* exposure	Specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed (…). Excludes other above-mentioned health hazards. *Category 1:* Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure *Category 2:* Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure *Category 3:* Transient organ effects.	(not detailed)
Specific target organ toxicity (STOT) – *repeated* exposure	Similar definitions as STOT-single exposure, replacing "single exposure" by "repeated exposure" and without category 3.	(not detailed)

Other hazards: Aspiration hazard, skin corrosion/irritation, serious eye damage/irritation…	Not detailed here	(not detailed)
Endocrine Disrupting properties that may cause adverse effects *in humans*	An active substance, safener or synergist shall be considered as having endocrine disrupting properties that may cause adverse effect in humans if [...] it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant to humans: • it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences; • it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system; • the adverse effect is a consequence of the endocrine mode of action.	*No exposure* (plant protection products; biocides for the general public); *no risk and use in conditions excluding contact with humans* and release into the environment (other biocides); can be *subject to authorization* (REACH). *Limit weight of 0.1%* (medical devices). No general restriction in other areas (see Table 7).
Environmental hazards		
Endocrine Disrupting properties that may cause adverse effects *in non-target organisms*	An active substance, safener or synergist shall be considered as having endocrine disrupting properties that may cause adverse effects on non-target organisms if it (…) meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant at the (sub)population level for non-target organisms: • it shows an adverse effect in non-target organisms, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences; • (2) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system; • (3) the adverse effect is a consequence of the endocrine mode of action.	
Hazardous to the aquatic environment	Hazardous to the Aquatic Environment is differentiated into *acute aquatic toxicity* and *chronic aquatic toxicity*. *Acute aquatic toxicity* means the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance. *Chronic aquatic toxicity* means the intrinsic property of a substance to cause adverse effects to aquatic organisms during exposures which are determined in relation to the life-cycle of the organism.	(not detailed)
Hazardous to the ozone layer	Not detailed here	(not detailed)
Very persistent, and very bioaccumulative (vPvB) substances	A substance that fulfils the persistence and bioaccumulation criteria below shall be considered to be a vPvB substance. *Persistence* - A substance fulfils the 'very persistent' criterion (vP) in any of the following situations: (a) the degradation half-life in marine, fresh or estuarine water is higher than 60 days; (b) the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days; (c) the degradation half-life in soil is higher than 180 days. *Bioaccumulation* - A substance fulfils the 'very bioaccumulative' criterion (vB) when the bioconcentration factor in aquatic species is higher than 5,000. (REACH regulation)	
Health and environmental hazards		

Persistent, bioaccumulative and toxic (PBT) substances	A substance that fulfils the persistence, bioaccumulation and toxicity criteria below shall be considered to be a PBT substance. *Persistence* - A substance fulfils the persistence criterion (P) in any of the following situations: (a) the degradation half-life in marine water is higher than 60 days; (b) the degradation half-life in fresh or estuarine water is higher than 40 days; (c) the degradation half-life in marine sediment is higher than 180 days; (d) the degradation half-life in fresh or estuarine water sediment is higher than 120 days; (e) the degradation half-life in soil is higher than 120 days. *Bioaccumulation* -A substance fulfils the bioaccumulation criterion when the bioconcentration factor in aquatic species is higher than 2 000. *Toxicity* - A substance fulfils the toxicity criterion (T) in any of the following situations: (a) the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms is less than 0,01 mg/l; (b) the substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B, or 2); (c) there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2). (REACH regulation)	

PART C: MANAGING THE RISK INCURRED BY EDs – WHAT COULD BE FURTHER DONE IN THE EU?

4 IDENTIFICATION OF ENDOCRINE DISRUPTORS

KEY FINDINGS

- Currently for EDs, the EU regulation lacks coherence, both within sectors and between sectors. It ignores several key scientific facts, including the widespread exposure to known and suspected EDs in the European population. It is therefore inefficient to protect human health.
- The general objective of the minimization of ED exposure and body burden in the EU population is a pertinent central goal of the EU ED regulation. Such an aim has been put forward by the 2018 Commission's communication towards a comprehensive EU framework on ED and is coherent with the 7th Environmental Action Programme.
- Attaining this goal requires a) a cross-sectorial definition of EDs (currently it only exists for plant protection products and biocides); b) a guidance document (further to that for plant protection products and biocides) explaining how to apply the definition on the basis of tests results and scientific literature to identify EDs; c) tests covering all ED modalities; d) legal requirements to make these tests compulsory in application dossiers; e) a management logic, which may distinguish sectors with very likely human exposure from those for which exposure is not systematic.
- Test development: there is an urgent need, not only to accelerate test development and validation, especially in areas beyond E, A, T, S (which are currently insufficiently covered, in particular for the thyroid axis), but also for regulators to use academic publications when assessing ED properties.
- Test requirements: As noted in the previous chapter, the regulatory texts setting out the content of application dossiers generally do not require tests that would allow to assess scientifically if the substance under evaluation is or is not an EDs. A logical and essential step would be to modify all regulations setting test requirements in sectors for which specific conditions apply to EDs, and include provisions allowing to make sure that dossiers will contain test results allowing to conclude if the evaluated substance or product is an ED.
- Research: In addition to the needs related to test development, six research areas should be considered as priorities: (i) epigenetics; (ii) effects across generations; (iii) ED effects on the microbiome, (iv) Green (safe) chemistry; (v) ED modalities beyond E, A, T, S and metabolism, (vi) Characterization of dose-response functions for ED effects in humans.

4.1 Gaps in the current regulation and general considerations regarding possible improvements

4.1.1 The regulation does not allow minimizing the health risks incurred by EDs

The review of compounds with suspected or very likely ED properties (chapter 2) has highlighted that recognized or suspected EDs are found in all media (diet, air, water), sectors (plant protection products, biocides, drugs, food, cosmetics, REACH chemicals…), in the general population as well as in occupational settings. The production, importation and marketing of several EDs have been forbidden in the past, mainly for persistent EDs such as DDT or PCBs, but precisely due to their persistence, the contamination of the diet and of the bodies of EU citizens is still widespread more than thirty years after their ban ([43] and references therein). The use of DES in pregnant women was banned over 40 years ago;

DES is not a persistent compound and is quickly eliminated by the body. However, due to its long-term effects in the subjects exposed *in utero* and in their offspring, today many "DES daughters" and DES "grand-children" suffer from the use of the drug [15, 16]. This illustrates how crucial the step of identification of hazards *before* the marketing of substances is, and that, however important, any system of identification of hazards of already marketed substances, will only be a second line of defence that can only alleviate part of the health and environmental burden incurred by EDs. As outlined in the 7th Environmental Action Programme, efficient identification of hazardous substances *before* their being put on the market should be the main approach, in particular in the context of possible irreparable health effects, limited means for post-authorization controls and complex compensation judiciary procedures.

In addition, many substances still authorized today represent a risk for the EU population and the environment because of their endocrine-disrupting properties.

As can be seen from Table 2 (section 1.8), some potential EDs are also possibly carcinogenic or toxic for the reproduction, so that they would also belong to the CMR hazard classes. However, this does not imply that a specific regulation for the ED hazard category is superfluous; indeed, first, the regulation of CMR substances in the EU does not always provide a relevant protection of the health of population, as can be seen from the ongoing population impacts of recognized carcinogenic substances such as particulate matter or benzene [260]; second, more than half of the substances currently recognized as substances of very high concern because of their endocrine-disrupting properties as part of REACH regulation are not simultaneously recognised as carcinogen, mutagen or toxic for the reproduction.

Finally, "safe thresholds" are unlikely to generally exist for EDs. Current regulatory tests may identify experimental thresholds for EDs, but these are expected to represent the limit of sensitivity of the test rather than constitute a biological threshold valid in human populations in their diversity (see 2.9 above).

4.1.2 The heterogeneous regulation of EDs in different sectors is hard to justify scientifically

Up to now, EDs have generally been managed heterogeneously. For instance, the EU has banned bisphenol A from food containers for infants and young children with the aim of reducing the exposure of this sensitive population. However, since bisphenol A crosses the placenta, exposure to bisphenol A starts at conception, nine months or more before any exposure through postnatal diet may occur, e.g. via the contamination of the diet of the pregnant woman or of consumer products used by her. In this context, the regulation that applies is the tolerable daily intake of bisphenol A, currently set at 4 µg/kg body weight per day, which assumes a lack of effect of bisphenol A in animal experiments below 400 µg/kg body weight per day. This tolerable daily intake is most probably too high to guarantee protection of health, given that many studies documented effects of bisphenol A on sensitive endpoints in the 5-10 µg/kg body weight per day range [120, 121], a range of doses where currently internationally agreed tests used in application dossiers for authorization are apparently not sensitive enough to detect adverse effects of bisphenol A.

Another example is that EDs are banned in plant protection products and biocides, but not generically banned in cosmetics. Their presence in cosmetics can entail exposure of pregnant women and foetuses.

4.1.3 Even within specific sectors, management of EDs generally lacks coherence

The regulatory sector with the most advanced regulation on EDs is that of pesticides; here, a management logic (no exposure to pesticides containing EDs) has been put forward as early as 2009; scientific criteria defining EDs have been set (with validity as of 2018) and a guidance document explaining how to apply these criteria on the basis of test results has been developed by the relevant agencies in 2018 [255], quickly after the scientific criteria were made available. However, it is unclear that this will be enough for

the spirit of the law to be applied. Specifically, given that the specific regulations listing the tests required in pesticides application dossiers for authorization do not make the tests listed in the 2018 guidance document compulsory, it will be difficult to assess if the substance is an ED or not (see 3.2.4). This means that a key element of the chain required for the regulatory logic set out in the 2009 PPPR regulation to be applied is missing (see 3.2 for details).

The situation is equivalent or worse in other key sectors mentioning EDs, such as REACH chemicals or cosmetics (see Table 7 for an overview). In several sectors with high potential for widespread human exposure, the hazard category of EDs is not even considered: this includes food additives, food contact materials, toys and workers' protection.

There are surely historical or political reasons for this lack of coherence, but the situation seems hard to justify from scientific and public health standpoints, especially when considering the core principles of the EU such as the Precautionary principle and the 7th Environment Action Programme.

4.1.4 In the past, important decisions have been delayed by lack of proper application of policies on conflicts of interest

In several instances, important regulatory decisions have been postponed or modified by what had been described as a "*scientific debate*", but that appears to be more similar to what the environmental humanities literature [261] refers to as "manufactured doubts", most often by scientists with probable conflicts of interests. This is in particular the case of the postponement of the publication of draft criteria defining substances with endocrine disrupting properties prepared by DG Environment in 2013, as requested by the plant protection products regulation of 2009. This planned publication has been cancelled following several events, including an open letter to the Chief scientific advisor of the President of the European Commission, that was later published in an editorial in 14 scientific journals [262]. Many of the authors were the editors of the journals where the editorial was published and turned out to have conflicts of interest (such as support from industries producing substances likely to be EDs), which were not reported. Similarly, on several occasions, scientists were invited to talk about EDs in EU institutions without being asked to report any potential conflict of interest. It has been scientifically demonstrated in several areas that scientists with potential conflicts of interest or studies on environmental factors supported by actors who may benefit from the use of the factor are far less likely to conclude about the existence of a hazard link to this factor than independent studies [263]. See also Annex 3 page 102.

It is striking to note that, during meetings, hearing or debates organized by or in EU institutions such as the European Parliament or the European Commission, scientists invited to talk are not always obliged to fill in conflicts of interest forms nor to declare any potential conflict of interest at the start of their talks or statements. This would not be the case in similar institutions in other parts of the world, such as the USA.

4.1.5 Translating scientific knowledge into regulation

The key scientific facts (see chapters 1 and 2) and regulation of EDs in the EU reviewed in this report demonstrate a need for regulation to be more coherent and consistent with scientific knowledge, thereby facilitating the overarching aim of minimizing the health impacts of EDs among EU citizens (as set out in the 7th Environment Action Programme and reiterated in the Commission communication towards a comprehensive EU framework on ED [101]). **We suggest this aim to be made concrete by explicitly setting the general objective of the minimization of ED exposure and body burden in the EU population as a central goal of the EU regulation.**

Several regulatory decisions, listed below, should trickle down from this aim:

a) The recognition of endocrine disruption as a hazard of similar concern to that of CMR (carcinogens, mutagens, toxics for reproduction) substances;

b) The requirement to avoid or minimize exposure to (known or presumed) EDs.

Point a) is a principle of REACH regulation, in the context of identifying substances of very high concern requiring authorization, while b) is explicitly written in the PPPR and currently only applies to plant protection products and biocides recognized as EDs, and should be extended to sectors where consumer exposure is most expected, i.e. on cosmetics, food additives, food contact materials and toys.

c) To ensure there is a unique (cross-sectorial) definition of EDs, distinguishing known EDs (level 1A), presumed EDs (1B) and suspected EDs (2) [47]. This definition could be written down in the CLP regulation, which defines the main categories of health hazards (see Table 8).

d) To provide a guidance document explaining how to check if a substance or a mixture is an ED on the basis of the scientific definition and of test results; ideally, such a document should also be cross-sectorial, but sector specific provisions are to be expected (e.g., in the case of cosmetics, for which animal testing is banned);

e) To make sure that all tests required in the guidance document are made compulsory for any application dossier for authorization, so as to facilitate ED identification;

f) In the case of sector-specific assessment, to ensure that the recognition of a substance as an ED in a sector automatically entails its recognition as an ED with the same level of evidence in all other sectors.

g) To extend the "no exposure to EDs" logic present in the pesticides regulations to all other use sectors for which human exposure is likely, in particular for industrial REACH chemicals with consumer uses, e.g., cosmetics, food additives, food packaging, toys, with the exception of drugs for which a specific logic is required;

It is important to recall in this context, given the scientific knowledge on specific actions of EDs (low dose effects, possible non-monotonic dose responses, cumulative effects often expected from combined exposure and vulnerable periods of exposure) that it is unlikely that safe levels can be set. In consequence, if a substance is an ED, an "authorized level" (or risk assessment) logic needs to be to be replaced by a no exposure logic.

h) To define a management logic for EDs in all media-oriented regulations (such as the water directive, food contact materials) following the principle of minimization of exposure to EDs outlined for all sectors for which human exposure is very likely (see 5.2 below);

i) To inform EU citizens about the presence of recognized or suspected EDs in all types of consumer goods (in particular through labelling) and possibly environmental media;

j) To ensure that any potential conflict of interest is declared by anyone communicating with an EU institution.

The issues related to the management of EDs are discussed at greater length in chapter 5; we discuss in this chapter those related to the identification of EDs.

[47] In practice, it would seem logical for such a definition to be written down in a law defining the other main categories of (health) hazards, such as CMR substances, with validity not restricted to a specific sector such as REACH chemicals or cosmetics or pesticides – this would correspond to the CLP regulation.

4.2 Towards a cross-sectorial definition of EDs

4.2.1 Assessment of the approved criteria for ED Identification under EU Regulations on Plant Protection Products and on Biocidal Products

In November 2017 and April 2018, the European Commission published regulations setting out scientific criteria for the determination of endocrine-disrupting properties in the areas of plant protection products and biocides [253, 254].

These publications result from provisions of the 2009 Plant Protection Product Regulation (PPPR) and the 2012 Biocide Products Regulation (2012) that specified provisions regarding the way plant protection products and biocides containing substances with endocrine-disrupting properties should be managed, without explaining how such substances should be defined and identified. The PPPR and BPR stipulated that "No later than 13 December 2013, the Commission shall adopt delegated acts in accordance with Article 83 specifying scientific criteria for the determination of endocrine-disrupting properties" [264]. With four years of delay, these criteria were published as a Commission Delegated Regulation for the BPR in November 2017 [253] and a Commission regulation in April 2018 for the PPPR [254]. The following year, ECHA, EFSA and the JRC provided a guidance document [255] describing how to perform hazard identification for endocrine-disrupting properties following the scientific criteria adopted in 2017 (this guidance document is discussed in 4.3.1 below).

The ED criteria for plant protection products and biocides is a document containing two sections. Our short discussion specifically refers to the text agreed for the PPPR.

In accordance with the PPPR and BPR, two definitions are actually provided, one for substances with endocrine disrupting properties that may cause adverse effects in *humans* (see 3.2.2 p.59) and one for substances with endocrine disrupting properties that may cause adverse effects on *non-target organisms*.

Although the recitals of the ED criteria acknowledge the need to identification of known and presumed EDs [253, 254], no categories of substances with endocrine disrupting properties distinguished according to the level of evidence are defined.

The criteria acknowledge the relevance of WHO definition of EDs (see 1.2). The criteria still deviate to some extent from this definition, e.g. by referring to the concept of "endocrine mode of action"

The criteria require the adverse effect to be a consequence of the endocrine mode of action, which reads as a very strong requirement. However, it is indicated below this statement that "the link between the adverse effect(s) and the endocrine mode of action shall be established based on biological plausibility", which seems more relevant.

When it comes to the assessment of the existing evidence to determine if the criteria are fulfilled, the text calls for reliance on a weight of evidence approach, which is relevant and may allow selective consideration of a part of the literature (e.g., lack of consideration of academic studies).

The criteria further call for reliance on the concept of "limit dose". This should not be used by applicants to limit testing to "low" doses, as focusing only on very low doses may require increased numbers of animals, in order to have sufficient statistical power (see 2.9 and Figure 12).

4.2.2 Definition of EDs

We suggest that a definition of EDs be adopted as part of the EU regulation, with validity in all sectors. This definition could be written down in the CLP regulation, that already defines CMR substances and other hazards.

A simple option would be to use the widely accepted WHO definition of EDs.

An alternative would be to rely on the phrasing in use for plant protection products and biocides [253], with the following adaption that relies on the interpretation provided in section 3 of ECHA-EFSA guidance document:

> A substance or mixture shall be considered as an endocrine disruptor if it meets all of the following criteria:
>
> (1) it shows an adverse effect in an intact organism or its progeny or in (sub)populations, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;
>
> (2) it shows endocrine activity;
>
> (3) there is a biologically plausible link between the adverse effect and the endocrine activity.

Point (1) is from the biocide ED criteria [253], adding the reference to *(sub)populations*, which are important to point e.g. to effects such as a modification of the sex ratio that are not adverse effects at the individual level; point (2) is inspired from ECHA-EFSA guidance document [255], which rightly suggests to delete the reference to the concept of mode of action before referring to endocrine activity. Point (3) is taken from ECHA-EFSA guidance document [255] without repeating the explanation "i.e. it has the potential to alter the function(s) of the endocrine system".

Before moving to the issue of the identification of EDs (see 4.3), we discuss the relevance of additional definitions for substances for which the level of scientific evidence is lower.

4.2.3 Definition of presumed and suspected EDs

From a scientific perspective, it is common and relevant in environmental and health sciences to categorize the level of evidence regarding an effect or a phenomenon. For example, IARC, the International Agency for Research on Cancer, classifies possible carcinogens in four categories (plus a category corresponding to substances that are probably not carcinogenic), while in the EU, there are three categories of carcinogens (see Table 9).

It would therefore be relevant to define *presumed* and *suspected* EDs. We make the following suggestions:

Presumed endocrine disruptor:

> A presumed endocrine disruptor is an exogenous substance or mixture that possesses properties that are likely to lead to endocrine disruption in an intact organism or its progeny, or (sub)populations.

Suspected endocrine disruptor:

> A suspected endocrine disruptor is an exogenous substance or mixture that possesses properties that might lead to endocrine disruption in an intact organism or its progeny, or (sub)populations.

Note that this latter definition corresponds to the definition of a *potential* endocrine disruptor from WHO [252] and from the Scientific Committee on Consumer Safety SCCS (SCCS/1544/14), but we suggest to use *presumed* ED instead of *potential* for consistency with the EU categories of carcinogens.

Table 9: Suggested hazard categories and criteria for endocrine disruptors and parallel with carcinogens.

Hazard category	Criteria for endocrine disruptors	Criteria for carcinogens*
1A	**Known endocrine disruptors** Substances known to have endocrine-disrupting properties, i.e. Showing an adverse effect in an intact organism or its progeny or (sub) populations; Showing endocrine activity; there is a biologically plausible link between the adverse effect and the endocrine activity	**Known carcinogens** Substances *known* to have carcinogenic potential for humans A substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. Category 1A: Classification is largely based on human evidence.
1B	**Presumed endocrine disruptors** Substances *presumed* to have endocrine-disrupting properties (lower level of evidence than 1A)	**Presumed carcinogens** Substances *presumed* to have carcinogenic potential for humans (lower level of evidence than 1A)
2	**Suspected endocrine disruptors** Substances *suspected* to have endocrine-disrupting properties (lower level of evidence than 1B)	**Suspected human carcinogens** Substances *suspected* to have carcinogenic potential for humans (lower level of evidence than 1B)

*Taken from CLP regulation.

4.3 A guidance document is needed to explain how test results and literature should be used to apply the ED definition

A guidance document based on the criteria defined in Regulations (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively, was published in 2018. We discuss this document and then explain why and how a guidance document covering most or all sectors will be needed once a cross-sectorial definition of EDs has been adopted.

4.3.1 Assessment of the EU's Guidance document for the implementation of the New Criteria on Endocrine Disruptors for Plant protection products and Biocides

In the authors' opinion, ECHA, EFSA and the JRC are to be commended for their compiling of this Guidance document. The guidance document provided (in its section 3) interpretations of the original ED criteria, which are relevant and that we suggest to use in any future (cross-sectorial) definition of EDs (see 4.2.1 above).

There are many excellent aspects to the document, if it is used and applied correctly. Most problems can be expected to arise from data gaps in testing and testing requirements (which are beyond the scope of the guidance document). It should be noted that the ED criteria state that the identification should be done mostly on the basis of existing data. This means that there is very little encouragement to generate new data, which could represent a major drawback. The identification of ED properties cannot be done on the basis of existing data for most chemicals, not even with systematic review methodology. Different national regulatory bodies have already underlined this fact. The Danish EPA and their French equivalent

(ANSES) noted that failures to identify EDs most often arose from incomplete files due to unclear testing requirements.

Further points need to be made:

(i) That the guidance document is currently restricted to Oestrogen, Androgen, Thyroid and Steroids (E, A, T, S or EATS). However, it should be noted that thyroid disruption is the focus of an appendix (Appendix 1). This reflects the difficulty of assessing not only thyroid disruption but also the potential effects of brain development that can ensue from disruption of thyroid signalling. That the main text focuses on steroid hormones is understandable given that current data and research are largely focused on these areas and that the discipline first evolved from work on reproduction. However there, as research progresses in non-EAS fields, results will need consideration and incorporation. There are 48 nuclear receptors in humans, many of which are poorly investigated. Progress can be expected on each.

(ii) Certain recommendations are highlighted (boxed) in the text (e.g. pp 20, 37, 40 and 42). Notably, on page 40, the box highlights the need to consider biological plausibility in the analysis, potentially obviating the need for identifying with certainty a mode of action, which is relevant as already mentioned.

(iii) Appendix 1 (Additional consideration on how to assess potential thyroid disruption for human health) is a critical and integral part of the document. Given the increase in neurodevelopmental disease and even taking different multifactorial drivers into account, the fact that maternal thyroid hormone is determinant of the foetus' brain development and the child's IQ is established [29]. Thus, a number of recommendations in the Appendix need to be underlined. Page 102 states that even though thyroid signalling is conserved across vertebrates, rats and mice (the most commonly used toxicological models) do display certain species-specific differences, so the document emphasises the need to interpret data by applying three recommendations including the idea that in the absence of specific proof to the contrary "humans and rodents are considered to be equally sensitive to thyroid disruption". Similarly, the section referring (page 103) to hazard assessment of decreases in T_4 (thyroid hormone) in adults, "in the absence of adverse histological changes should act as a trigger for further studies".

Given the recommendations on developing new tests (see 4.5), there will be a need to revise the current guidance document for plant protection products and biocides regularly.

4.3.2 A cross-sectorial guidance document will be needed once a cross-sectorial definition of EDs is enforced

In general, subsequent requirements to update and adapt this document will be required on a number of fronts:

- On non-EATS mechanisms
- For applications to other regulatory scenarios. This will be particularly difficult for cosmetics where animal testing is not permitted. Adverse effects are most often identified in animal tests (and human epidemiology). Given that adverse effects need to be demonstrated and related to the endocrine mode of action for EDs in cosmetics this conundrum needs to be resolved. One approach is to use free-living embryos at the in vitro / in vivo interface. This approach is exploited in one of the 8 research proposals currently funded in the ED screening call (see 4.5).

Once definitions of known EDs, presumed and suspected EDs have been published, the guidance document should be updated and expanded to cover all regulatory sectors. Specific issues will need to

be considered, such as the identification of EDs for substances only used in cosmetics, a sector in which animal testing is not permitted.

4.4 Setting and enforcing coherent test requirements

One of the key conclusions of the description of the current EU regulation regarding EDs is the lack of coherence between and also within sectors (see chapter 3). In particular, already mentioned, even for sectors where some management logic specific to EDs is specified by the regulation (plant protection products, biocides, REACH chemicals), it appears that the regulatory texts setting out the content of application dossiers generally do not require tests that would allow to scientifically assess if the substance under evaluation is or is not an EDs.

It is our perception that, in many cases, in particular in the situation of the re-evaluation of a substance that is already on the market, even if additional information are requested to the applicant, not having the information allowing to assess if a substance is an ED will, at least in the short term, have it handled as a substance that is not an ED (that is, unclassifiable substances will, at least for some duration, be handled as non-hazardous substances, which will result in increased population exposure and possible health impacts if the substance turns out to be hazardous).

A logical and essential step would be to modify all regulations setting test requirements in sectors for which specific conditions apply to EDs, and include provisions allowing to make sure that dossiers will contain test results allowing to conclude if the evaluated substance or product is an ED. Of course, evaluation dossier from any sector need to be easily made available to assessors from all other sectors.

If EDs become regulated in additional sectors (see chapter 5), then as the regulations setting up the management logic of EDs, the specific directives listing the test requirements for the authorization of products or substances in this sector should be updated to make sure that all application dossiers contain the information allowing to classify the substance in one of the ED categories. In particular, the specific regulations listing test requirements for REACH chemicals, cosmetics, food additives and packaging, toys, should be expanded to take (more) efficient consideration of EDs and allow their identification in each sector. Identification of a substance in one sector should trigger automatically its recognition as an EDs in all other sectors.

Finally, there should be controls on application dossiers to identify misconducts in the preparations of dossiers (e.g., lack of reporting of a test that had turned out positive, selective reporting of test results or falsification of test results) and sanctions should be planned and implemented to discourage such misconduct.

The test requirements should be defined by ECHA, EFSA and any other relevant authority keeping in mind the above-mentioned issues and making sure that all ED modalities and all potential ED endpoints (including those related to alterations of brain development) are well covered.

4.5 Test development

There are many identified ED modalities (i.e., ways whereby a substance can alter the activity of the endocrine system), including the endocrine, androgen, thyroid, steroid (E, A, T, S) modalities, as well as modalities related to other nuclear receptors (see chapter 1). Currently, internationally validated guidelines related to EDs in the context of mammalian toxicology focus on oestrogen, androgen, aromatase activity and, to a lesser extent, thyroid modalities. These tests are not perfectly sensitive and some provide variable results with variations in protocols within the guidelines (e.g., depending on the animal model used or route of exposure [251]); as already mentioned, in the case of identification of

oestrogenic activity, the test relies on changes in the weight of the uterus of exposed animals, while oestrogenic effects can happen without the weight of the uterus being affected [250].

Thus, better and more efficient test methods are required, especially in a number of under-investigated areas, including thyroid disruption and disruption of hormone synthesis and metabolism, beyond aromatase activity.

The lack of specific tests for thyroid and related neurodevelopmental adverse effects led to a series of OECD scoping meetings on the topic, resulting in two reports in 2014 and 2017 [48]. These OECD reports focused on in vitro and ex vivo (cell-based screens) that could eventually be used for high throughput assays. In 2017/18, DG Environment spearheaded a thyroid Expert Group focused on improving endpoints in the currently validated OECD in vivo assays. The meetings underlined the urgency of the need for better tests (and validation of those tests) to assess the multiple levels through which EDs could affect thyroid signalling and brain development. Many of the conclusions of the thyroid expert group are reiterated in the thyroid appendix of ECHA/EFSA Guidance document [255].

In 2017-2018 the EU Commission launched a research call (*SC1-BHC-27-2018: New testing and screening methods to identify endocrine disrupting chemicals*). Researchers were asked to develop novel, faster and more effective screening methods using both in vivo, in vitro and in silico approaches. Proposals were invited to focus on the "most urgent regulatory needs" in five main areas: thyroid disruption, developmental neurotoxicity, female reproduction, metabolism and non-genomic carcinogenicity. The eight successful projects started in early 2019 for five years. Further, it was specified that the tests developed in the proposals should be taken through to validation by the OECD.

However, the process of test guideline validation by the OECD is long, often being in the order of ten years. Most often it involves a succession of ring tests, i.e. a series of tests on a selected number of active and inactive controls (at different doses) carried out in independent or industrial (often industry contract laboratories) in different OECD countries. The results are subjected to statistical analysis and then the process repeated up to three times, often extending the number of substances tested. One of the main problems is that the country proposing the test has to find the financial and infrastructural resources to carry the tests out, which in the current economic climate can be challenging. France for instance, being aware of this problem, has proposed a national centre for ED testing and validation in its ED strategy on EDs.

Hence, there is an urgent need, not only to accelerate test development and validation, especially in areas beyond E, A, T, S (which are currently insufficiently covered, in particular for the thyroid axis), but also for regulators to use academic publications when assessing ED properties as clearly stated in the ECHA-EFSA Guidance Document [255].

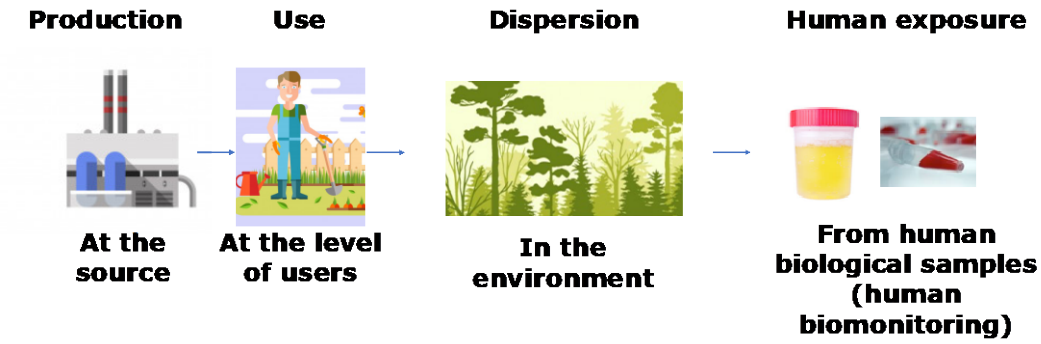
A full guide to the tests currently validated by the OECD is given in their recently updated document [99]; see also Table 5.

4.6 Surveillance of ED production, use and exposure

Monitoring of suspected and proven EDs and of hazardous substances can generally be done at different levels, from their production, to the environment and the human body (Figure 16).

[48] http://www.oecd.org/publications/new-scoping-document-on-in-vitro-and-ex-vivo-assays-for-the-identification-of-modulators-of-thyroid-hormone-signalling-9789264274716-en.htm
https://doi.org/10.2779/921523

Figure 16: Schematic fate of man-made chemicals from their production site to the human body illustrating the possible different levels of monitoring of chemicals.



4.6.1 Monitoring of ED production and use

Monitoring of production and use of EDs and suspected EDs is of central importance. The implementation of REACH regulation has provided an estimate of the number of chemicals currently marketed in the EU, outside specific sectors such as plant protection products, biocides or cosmetics. Currently, about 15-20,000 compounds have been registered by REACH, but other substances still lack information for registration[49]. Overall, the EU institutions lack detailed information on the volume of chemicals produced or used, including proven or suspected EDs or CMRs. Such information should be collected and made available by the relevant industry and activity sectors, with a fine level of detail (that is, on a compound by compound basis, on a time scale of a year or less, and at a spatial scale finer than the country). For example, datasets on pesticides production, sales and use, distinguishing between each pesticide and at a fine spatial scale regarding the use, should be developed and made available (such databases exist e.g. in California[50]).

4.6.2 Environmental monitoring of EDs

Environmental monitoring of selected EDs should also be performed, in a harmonized way at the EU scale. This should include monitoring of drinking water, which is currently conducted but without targeting EDs specifically and without data being centralized, standardized, cleaned and made accessible at the EU level. It may not be relevant or possible to assess a large number of EDs on a regular basis in all water networks, so that the monitoring of the overall oestrogenic, androgenic, thyroid… activities could be monitored, instead of providing a list of substances.

4.6.3 Human biomonitoring of EDs and hazardous chemicals

Crucially, human biomonitoring should be conducted at the EU level for a large list of hazardous or possibly hazardous substances, including EDs. This information is an essential complement of the former approaches since the levels of chemicals in body fluids, such as urine or blood, constitute an integrated measure of exposures from various environmental compartments (drinking water, diet, air, the occupational setting…). Standardized approaches, both in terms of recruitment of the population and analytical approaches, should be used, taking example from NHANES, the biomonitoring survey

[49] https://echa.europa.eu/fr/-/registration-numbers-granted-to-32-515-reach-2018-registrations and https://echa.europa.eu/documents/10162/13628/evaluation_report_recommendations_2017_en.pdf/c2cb9cd3-e2b5-662a-c359-c5d998444853

[50] https://calpip.cdpr.ca.gov/main.cfm

conducted in the USA by the American Centers for Disease Controls[51] and drawing all required lessons from attempts to conduct harmonized biomonitoring in the EU, such as the current HBM4EU H2020 project[52]. The volume of biospecimens collected in each subject and sensitivity of the analytical methods used should allow simultaneous assessment of a large number of chemicals in order to characterize combined exposure. A fraction of each sample should be kept frozen to allow future assessment of new substances as knowledge evolves.

4.7 Consideration of potential conflicts of interests in events organised with scientists in EU institutions

Any scientist invited to present his opinions in an oral or written form in an EU institution or to a member of such an institution should declare any potential conflict of interest. This is not intended to discourage scientists working for the industry to bring in their expertise, but aims at allowing to better distinguish true scientific controversies from disagreements between academic and regulatory science, or academic science and industry. This would be merely the translation at the level of the highest institutions of rules that now apply to any scientist working or bringing expertise to an EU agency. In practice, this would imply to request to fill in conflicts of interest form before any meeting, to start any scientific presentation by a statement of the potential conflicts of interest, or a lack thereof, and to mention any potential conflict of interest in reports or documents sent to an EU institution.

4.8 Key research initiatives to be supported

In addition to the needs related to test development, five research areas should be considered as priorities: (i) epigenetics; (ii) effects across generations; (iii) ED effects on the microbiome, (iv) Green (safe) chemistry; (v) novel ED modalities and (vi) characterization of dose-response functions for ED effects in humans.

4.8.1 Epigenetics

Many EDs act through modulation of epigenetic processes. Epigenetics means literally "above the gene", i.e. changing when and where genes are expressed in different tissues and at different time points without modifying or mutating the sequence of DNA. Epigenetic effects most often implicated either DNA methylation or changes in chromatin structure (chromatin being the proteins surrounding the actual DNA sequence) and can be referred to as nongenomic.

Epigenetic effects can be limited to a given cell or maintained as the cell divides and differentiates, thus, nongenomic or epigenetic effects are to be expected in situations where a foetus, child or adult is exposed. Similarly, in the case of exposure during pregnancy the foetal sperm or eggs cells can also undergo epigenetic changes that will result in adverse effects in the grandchildren of exposed mothers. This has been demonstrated for DES exposure [15].

Epigenetic regulatory mechanisms characterise many nuclear receptor responses, including the most studied, the E, A, T, S. A key example can be found in thyroid hormone action. Besides its role in human brain development, thyroid hormone also orchestrates transformation of a tadpole into a frog. Tadpoles and frogs share the same genome, the same genetic information, but the way the information is expressed is different in the frog and the tadpole giving them a different phenotype (morphology and physiology). The changes induced by thyroid hormone are principally epigenetic modifications. The field

[51] https://www.cdc.gov/exposurereport/index.html
[52] https://www.hbm4eu.eu/the-project/

of epigenetics has exploded over the last 20 years and how EDs (alone and in mixtures) affects these gene regulatory mechanisms needs to be better examined.

4.8.2 Multi- and transgenerational effects

As explained above, epigenetic effects have been demonstrated for three generations subsequent to exposure during pregnancy. However, whether exposure to EDs can affect subsequent generations, demonstrating transgenerational effects beyond the population directly exposed requires more research, both in terms of the potential mechanisms implicated and in terms of disease categories. In some cases, as mentioned in section 1.9, animal studies have demonstrated clear transgenerational effects of EDs beyond the "grandchildren" of mice studied [55]. Transgenerational effects of a number of EDs have been shown in animal studies (including bisphenol A, PCBs, vinclozolin and DES), arguing for better understanding of the phenomenon. Potential mechanisms for transgenerational effects include different nongenomic mechanisms, mainly DNA methylation changes (see [66] for review of mechanisms implicated). The urgency of research in this area has recently been emphasised both in terms of human health [265] and for environmental concerns [266].

4.8.3 ED effects on the microbiome

The microbiome, represents an essential component of all our physiological, especially our immune responses [267, 268]. The genome of the multiple species that compose our microbiome is more complex than our own and is an integral part of our endocrine responses [269]. That certain EDs can affect the microbiome is known. One example is the biocide triclosan [270].

4.8.4 Green chemistry

Green chemistry is a broad subject with many journals already devoted to the topic. In the current context it can be defined as producing chemicals for which production methods require less energy and more importantly are readily biodegradable and less toxic to the environment and to human health than those in use today.

Replacing known EDs with others that can be equally harmful is often referred to as "regrettable substitution". An example is the possible replacement of part of the bisphenol A by bisphenol S or F, both of the latter having similar or worse ED properties (see for example [271]).

Hence, carrying out research for chemical substitutes for known, presumed or suspected EDs can fulfil two purposes each with strong socio-economic benefits. In the first place, finding less harmful, well-tested substitutes will enhance public health and reduce environmental risks. Second, the potential for innovation by the chemical industry will be a strong economic driver, similar to that seen for development of alternative energy sources that can create employment whilst encouraging sustainability [272].

4.8.5 EDs acting on less studied modalities beyond E, A, T, S and metabolism

As mentioned above (see for example chapter 1 and section 4.3) most current research is directed to adverse ED effects on reproduction through disruption of actions of the sex steroids, (e.g. oestrogen and androgen) and effects on brain development and metabolism whether through thyroid hormone or other related hormones. Hence, the focus in the current guidance document is on steroid hormones (mainly oestrogens and androgens). However, as amply emphasized, there at least 40 other nuclear receptors for hormones other than these, and their signalling pathways can also be implicated in reproductive, metabolic, neurodevelopmental disease as well as in other forms of non-communicable

disease such as immune disorders and allergies [273]. Examples include the Vitamin D receptor [274] and the vitamin A receptor [275]. Although nuclear receptors, with their capacity for ligand binding and control of gene transcription, are classically considered as the principle pathways for endocrine disruption, many other signalling pathways can be implicated even in classical endocrine signalling systems such as thyroid hormone (see for instance [276]). Potential research domains include non-canonical nuclear receptor signalling through membrane located receptors, diverse second messenger systems [277, 278] and microRNAs [279].

4.8.6 Characterization of dose-response functions for ED effects in humans

Dose response functions characterizing the effect of exposure to specific EDs or suspected EDs in humans are relevant to allow better identification of EDs. The accurate assessment of exposures in the relevant exposure windows, before occurrence of any disease, and control for potential confounding factors, which is important in the context of multifactorial diseases, is best obtained in longitudinal epidemiological cohorts.

This will require new types of cohorts with deep and accurate characterization of exposure to EDs, which, in the case of non-persistent EDs that are to be assessed via biomarkers, shall imply collection of repeated biospecimens in each subject [247].

5 MANAGEMENT OF EDS ACROSS SECTORS TO PROTECT HEALTH

KEY FINDINGS

- Better health protection could be achieved by recognizing EDs as a class of hazard of equivalent concern to carcinogens, mutagens and reprotoxicants in all sectors and not only for plant protection products, biocides and REACH chemicals.
- In order to minimize ED exposure among EU citizens, the EU should move towards an identical management of EDs across all sectors for which ED use is very likely to entail population exposure. This includes in particular, plant protection products, biocides, food contact materials, food additives, consumer goods, cosmetics and toys. Established scientific facts show that (a) hormones act at extremely low doses; (b) some recognized EDs also act at low doses; (c) there are methodological limitations to the approaches often used to identify so-called safe thresholds/ tolerable daily intakes in regulatory toxicology and (d) the approaches generally used to identify these safe thresholds generally do not consider cumulative effects of combined exposure. Hence, one option to protect human health and make the EU regulation more coherent across sectors would be to apply a logic similar to that already in use for pesticides, i.e. that substances identified as EDs or presumed EDs should not be authorized ("no exposure" logic).
- The oestrogenic, androgenic, thyroid, steroid (E, A, T, S) load of specific media such as consumer products, food and drinking water should be evaluated and monitored, and the implementation of limit values for E, A, T, S activities should be considered.

5.1 General strategy to manage the ED risk in all sectors and media

In complement to the development of a horizontal ED definition, an accompanying guidance document and implementation of relevant test requirements (see 4.3), a risk management logic needs to be defined for EDs in each sector.

The need to have a unique identification of EDs across sectors ("One chemical, one assessment") does not imply that the logic of management of EDs be the same in all sectors.

Our suggestion is to distinguish sectors on the basis of two main factors:

- The expected benefit of the family of products;
- The potential for widespread exposure in the general population or in sensitive populations.

The first factor would lead to much more stringent use of EDs in areas such as toys, food additives and food contact materials, than for drugs, which have a proven benefit.

The second factor would lead to distinguish the sectors for which human exposure to the chemicals present in the marketed products is very likely (e.g., food contact materials, food additives, cosmetics, toys, consumer goods) to sectors for which exposure is much less frequent. Similarly, media and places for which exposure is very likely (water, work place…) deserve specific consideration.

Here, we provide some suggestions for changes in the regulations reviewed in chapter 3.

5.1.1 Management logic for products used by consumers as part of REACH regulation

Currently, REACH regulation follows a logic according to which the substances belonging to specific hazard classes are to be put on an authorization list (the so-called Annex XIV of REACH, as well as Annex XVII), following which management decisions about the substance may occur. Annex XIV currently only includes 43 substances[53], which represents about one substance added to the authorization list every 400 substances[54]. The list of substances of very high concern currently includes 13 EDs, which is much lower than the expected number of known or presumed EDs. It is unlikely that the aim set forth in the 7th Environmental Action Programme, namely that "efforts need to be stepped up to ensure that, by 2020, all relevant substances of very high concern, including substances with endocrine-disrupting properties, are placed on the REACH", can be attained at this rate.

One suggestion for improvement toward minimization of ED exposure would be to revert the logic of entry in REACH authorization list for EDs in products with possible human exposure: that is, as soon as a substance or a product with potential exposure of the general population is identified as an ED or suspected ED (as a result of an evaluation conducted in any sector), the substance would not be authorized. Following requests from applicants, derogations could be evaluated and granted if deemed justified by the relevant authority. Note that, in order to follow the logic of equivalent concern for EDs and CMRs , such provisions would have to be also set up for products with potential general population exposure containing CMRs.

5.1.2 Management logic as part of REACH regulation – towards a clearer "equivalent concern" principle for CMRs and EDs

REACH regulation tends to set EDs on a similar level of concern to CMRs, but this logic is currently not followed because of 1) a lack of efficient tests requirements for EDs in REACH regulation (see chapters 3 and 4), and 2) a slightly different handling of EDs in the text of REACH regulation. A final consideration is that there is no official definition of EDs for this sector (or for chemicals' use in general, see 4.2)

Regarding point 2, the REACH regulation could be amended so that chapter 57 includes a specific bullet point setting EDs at exactly the same level as CMR , PBT substances, without the need to show that the specific ED *is* of similar concern to CMR, PBT or vPvB substances. In practice, this could be done by adding a bullet point after article 57.e stating:

- substances meeting the criteria for classification in the hazard class endocrine disruptor 1A or 1B in accordance with section … of Regulation (EC) No 1272/2008 [or any other relevant regulation where the definition of ED would be located];

and to delete reference to EDs in the current article 57.f.

5.1.3 Management logic for plant protection products and biocides

Although the recitals of the ED criteria for plant protection products and biocides call for the identification of known and presumed endocrine disrupting substances (as for known and presumed CMR substances, which are not authorized), currently only known endocrine disrupting substances are defined in the

[53] https://echa.europa.eu/fr/authorisation-list

[54] This calculation is based on the figure of about 17,000 substances registered in the context of REACH regulation reported by ECHA in its 2017 report (see https://echa.europa.eu/documents/10162/3048539/FINAL_MB_03_2018_(2)_General_Report_2017_MB49.pdf/d6c665cc-8c84-d33f-2f82-fa148e366f5d).

context of the plant protection products and biocides regulation. One should either make sure that the current definition and guidance document allows to cover known and presumed EDs, or that the plant protection products and biocides regulations, their annexes and the ECHA-EFSA guidance document to identify EDs in plant protection products and biocides, are updated to distinguish known and presumed EDs, thereby not authorizing plant protection products and biocides containing known and presumed EDs.

5.1.4 Management logic for cosmetics

In cosmetics, substances recognized as CMRs (categories 1A, 1B or 2) are banned. Following the principle of equivalent concern of EDs, a similar logic should be enacted in the cosmetics regulation for proven, presumed and suspected EDs. The inclusion of suspected EDs is important here, given that for substances only used in cosmetics, *in vivo* tests on animals are not authorized. As such tests could improve the level of evidence regarding ED properties, all evidence from other sectors must be made available and used.

5.1.5 Review of the cosmetics regulation by the European Commission (2018)

A review of the cosmetics regulation was published in November 2018 by the Commission[55]. It mentions that "Although these criteria [defining substances with endocrine disrupting properties in the context of the plant protection products and biocides regulations] do not have direct legal consequences for other areas of EU law than the areas of plant protection products and biocides, they should be taken into account, as far as possible, for the purposes of the present review of the Cosmetics Regulation."

The EC review further mentions that "substances identified as endocrine disruptors are currently subject to the general safety assessment of the SCCS. They are treated like substances of concern for human health and are subject to case-by-case regulatory action".

This approach is deemed relevant by the Commission: "Mindful of the different approaches taken in relevant pieces of EU legislation to address endocrine disruptors in different sectors, the experience collected since the entry into application of the Cosmetics Regulation has not revealed elements which would justify deviating from the regime designed by the legislator to address the safety concerns related to the use of endocrine disruptors in cosmetics."

The review concludes that "The Cosmetics Regulation provides the adequate tools to regulate the use of cosmetic substances that present a potential risk for human health and to take the appropriate regulatory measures based on a scientific assessment of available data concerning human health".

As already mentioned, a number of substances used for cosmetic and personal care products are known or suspected EDs. Examples include parabens, triclosan and benzophenones (see 2.3), which are authorized up to specific concentrations. This case-by-case logic deemed relevant in the November 2018 statement from the Commission stands in clear contrast with the logic in place for CMR substances present in cosmetics (*known*, *presumed* and *suspected* CMR categories), which is that of a ban on the hazard classes as a whole, case by case exemptions being possible. In the perspective of protecting health and the environment, it is not clear why CMRs and EDs are put on a similar level of concern in the plant protection products, biocides and REACH regulations and why this should not also be the case in the cosmetics regulation, which deals with a sector with expected human exposure, especially to vulnerable populations.

[55] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018DC0739&rid=2

In the same perspective, it is also unclear why EDs should be managed mostly on an "authorized level" logic in the cosmetics sector, while EDs are also treated under a no exposure logic for plant protection products and biocides sold to the general public.

5.1.6 Management logic other sectors with likely widespread exposure

In other key sectors with widespread consumers' exposure, minimization of risk could be attained through adopting a no-exposure logic, as for pesticides. This would be particularly relevant for toys, for which there should be no justification of use of any substance of very high concern, for food additives, food contact material, and possibly for consumer goods in general. For the latter sector, distinctions could be made between goods for which the potential for human and environmental exposure is very unlikely, for which strong restrictions may not be warranted, and goods for which there is potential for human or environmental exposure, e.g. through contact or migration.

In addition, we outline below some sector-specific provisions, together with a discussion regarding the labelling of products containing EDs.

5.2 Management of EDs in specific media including water

5.2.1 Management of EDs in water

In specific media such as drinking water, options include (i) the monitoring of all suspected EDs; (ii) the monitoring of a list of specific EDs and (iii) the monitoring of endocrine disrupting activity for specific ED modalities. The options are not mutually exclusive and can either be implemented in all drinking water networks or in a subset of monitoring networks deemed representative of the EU region considered.

In its 2018 proposal for a revised drinking water directive, the Commission suggested an approach leaning towards option (ii), limited to three recognized EDs (beta-oestradiol, nonylphenol, bisphenol A, see 3.5.1 above), termed as "representative EDs". Although it is relevant to monitor and limit their occurrence in drinking water, it would be optimistic to assume that three EDs could be representative of all EDs, that have very diverse sources, chemical nature, properties in water, and that this would be enough to quantify or efficiently limit the impact of ED from drinking water exposure.

A relevant additional step would be to also follow option (iii) above, consisting in monitoring oestrogenic, androgenic, thyroid disrupting activities (and possibly activity related to other ED modalities) in drinking water. This option is expected to cover a larger range of possible ED effects and to be much cheaper than monitoring a long list of EDs. If evidence of a very high activity of any ED modality (e.g., a high oestrogenic activity) is found in a given network, then more detailed investigations could be undertaken to identify the specific compound(s) that may cause this increased activity. Maximum levels for the main ED modalities and for the sum of all ED modalities could be set, as a way to minimize ED exposure from drinking water taking into account effects of combined exposures.

Such a logic is also worth considering for surface and ground waters.

Given the presence of EDs in the air, a reflexion on their monitoring and limitation, possibly considering the logic outlined here for drinking water, could be undertaken.

Drugs constitute a source of contamination of drinking water by EDs and other hazardous chemicals [56]. The options to limit the presence of EDs from drugs in water (treatment of water, specific collection and treatment of the urine of patients using specific drugs…) should be outlined and considered.

[56] See e.g. https://www.who.int/water_sanitation_health/diseases-risks/risks/info_sheet_pharmaceuticals/en/

5.2.2 Concerns regarding the use of paracetamol during pregnancy

Emerging scientific evidence raises concerns regarding the biological and possible health effects of use of paracetamol (acetaminophen) and other mild analgesics (e.g. aspirin, ibuprofen) during pregnancy, including early pregnancy (see 2.4). Paracetamol seems to be widely used during pregnancy in many EU countries, so that even a small effect at the individual level could have a large impact at the population level. The topic should be thoroughly expertized, then communication and possibly management measures considered to limit use in pregnant women.

5.3 Labelling of products containing EDs

Currently, it is only for cosmetics that consumers are informed about the chemicals present in the goods that they buy. Someone buying a garbage bag or a plastic bottle is generally not able to know if any biocide has been added to the bag or if the bottle has been manufactured using an ED. Even in cosmetics, the only information available corresponds to the list of chemicals used, which implies that probably few consumers are able to sort out if one of the many chemicals listed is present on a documentation listing all presumed EDs; such ability is not expected to be widely present in the population, and to be less frequent in specific (possibly sensitive) subgroups with little time such as parents with young children or socially disadvantaged subjects.

Until regulations such as the ones outlined in this chapter allowing to avoid or minimize the presence of EDs in consumer goods, the possibility of defining a label indicating the presence of EDs in a consumer good, and of making the use of such a label in all manufactured goods in which an ED or presumed ED is present should be considered.

5.4 Conclusion

After several decades of multidisciplinary research in endocrinology, ecotoxicology, toxicology, epidemiology, clinical research, epigenetics, environmental sciences and other disciplines, endocrine disruption is now a strong and validated scientific concept. Several key mechanisms have been identified whereby exogenous compounds or mixtures can induce adverse effects in humans or the environment through an alteration of the endocrine system. Hormones act at extremely low doses, and EDs are expected to also act at very low doses. The key organisational role of hormones during development makes it very unlikely for any threshold of action to exist for EDs. The multiple functions of the endocrine systems and its interactions with the immune and nervous systems explain why EDs can be implicated in such a wide range of diseases (see chapter 1).

Our review of the existing data on the presence of EDs in the environment and in the organism shows that EDs or suspected EDs are currently present in all media (water, diet, food contact materials, cosmetics…) and that the body of a large majority of EU citizens contains dozens of suspected EDs. This figure is expected to strongly increase if more detailed information on the use of chemicals in each sector are collected and EU-wide biomonitoring studies encompassing large numbers of chemicals conducted. The probable range of the corresponding societal costs for are exceptionally high, as is the price of inaction.

This evidence justifies to consider EDs as a specific class of hazard. The principle of assigning this new hazard category a level of concern equivalent to that of CMRs, currently present in parts of the EU regulation but not clearly enshrined, is totally well-founded.

Many areas of scientific uncertainty remain. These include the identification of additional modes of actions of EDs; the exact characterization of dose-response function and dose-response functions in human population; the identification of EDs among marketed and natural substances; the exact number

and list of EDs in our environment. Given the already proven effects of EDs and the number of substances that may turn out to be EDs, these uncertainties are incentive for further research. Similar types of uncertainties exist for other hazard categories such as carcinogens.

Although claims of the contrary have been made in the past due to loopholes in the procedures to limit conflicts of interest, the existing uncertainties are in no way reasons to postpone regulatory action, at least not for the substances that are most likely to be EDs.

The current regulatory procedures do not provide an efficient filtering of EDs allowing their identification and limitations of their use before they are marketed, nor is there any safety net to do so once they are on the market, which is anyway generally more expensive for society and less efficient. The current situation is clearly detrimental for the environment, human health, society, sustainability and most probably for our economy.

We have listed several possible regulatory actions, with many stemming from the identification of incoherencies in the current EU chemicals regulation. In key sectors with strong potential for human exposure to the products marketed, the regulation appears inconsistent. For example, in the case of the plant protection products, biocides and REACH regulations, the current regulatory test requirements are not sufficient to permit correct identification of EDs. Between-sector comparisons also point to striking inconsistencies. Indeed, while in some sectors for which there is strong potential for human exposure, EDs exposure is intended to be banned or strongly limited, the regulation of other sectors with very strong or certain likelihood of human exposure (such as that of food additives or food contact material or workers' protection) does not even mention EDs as a generic concern.

Regarding ED identification, making the regulation simpler and coherent (without reducing its efficacy), and closer to the aim of the 7th Environment Action Program, would require providing a (horizontal) definition of EDs based on the current scientific consensus that would be valid for all sectors. A second step would be to make sure that the provisions making it compulsory for all application dossiers for marketed substances to include information allowing to identify EDs are laid down in regulations. For transparency, coherence with the CMR regulation, and to account for the acknowledgment of uncertainties as well as the limitation of animal testing, the regulation should distinguish three categories of EDs, according to the level of scientific evidence (such as known, presumed and suspected EDs).

When it comes to risk management, the general aim of minimizing ED exposure has recently been put forward by the European Commission in its 2018 communication towards a comprehensive EU framework on EDs. This aim should not only be strongly integrated at several levels of regulations, but also be developed into concrete risk management decisions in most sectors relevant to chemicals, environment and health. We suggest specifically to distinguish on the one hand all sectors for which there is a high likelihood of human exposure (cosmetics, food, food additives, food packaging, cosmetics, biocides, REACH chemicals, consumer goods) from those with less likely human exposure. In the former sectors, an option would be not to authorize the substance.

Our recommendations will not lead to a ban of a large number of poorly characterized substances. However, they should strongly increase the level of knowledge on the hazards and safety of many substances, and would only lead to decreased use or ban for substances with evidence of an adverse effect and their use in products entailing exposure of the general population. Ultimately, this will improve health, better protect the environment and help to develop a sustainable economy.

RECOMMENDATIONS

1. **Policy goal:** Endocrine disruptors (EDs) are one of the main classes of health hazards and are of similar concern to carcinogens, mutagens, substances toxic to reproduction (CMRs), PBT (persistent, bioaccumulative and toxic) and vPvB (very persistent and very bioaccumulative) substances. Consequently, in order to better protect human health and the environment, on which our health depends, **the European Union should develop a set of trans-sectorial and harmonized regulations to minimize human and environmental exposure to endocrine disruptors.**
2. Attaining this goal requires a) a cross-sectorial ("horizontal") definition of EDs with three categories according to the level of evidence; b) a guidance document explaining how to apply the definition on the basis of tests results and scientific literature, and identify EDs; c) tests covering all ED modalities; d) legal requirements to make these tests compulsory in application dossiers; e) risk management measures aiming to minimize ED exposure, which may distinguish sectors with very likely human exposure from those for which exposure is rare.
3. **ED definition:** Currently EDs are only defined in the plant protection products and biocides regulations context. **EU regulation should include a definition of EDs valid for all sectors.** We suggest using the WHO definition, or the current EU definition with slight modifications: "Endocrine disruptors are defined as a substance or mixture that meets all of the following criteria: 1) It shows an adverse effect in an intact organism or its progeny or (sub)populations, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences; 2) it shows endocrine activity; 3) there is a biologically plausible link between the adverse effect and the endocrine activity." **Similarly to other hazards, such as CMRs, this cross-sectorial definition requires regulation to distinguish three categories according to the level of evidence: known (category 1A), presumed (1B) and suspected (2) EDs.**
4. **Guidance document:** A guidance document, based on that currently existing for plant protection products and biocides, should be developed to explain how EDs should be identified on the basis of this definition across sectors, including REACH chemicals, cosmetics, food contact materials and food additives. The currently existing logic requiring a weight of evidence approach that establishes the link between the adverse effect and the endocrine activity based on biological plausibility should be maintained.
5. **Test development:** there is an urgent need to accelerate test development and validation, especially for modalities beyond reproductive steroids, such as disruptors of the thyroid axis, and the related adverse effects. There is also a need to enhance use of academic publications when assessing ED properties.
6. **Test requirements:** Currently, there are insufficient data requirements in the regulation to be able to efficiently identify EDs in any sector, including for pesticides and REACH chemicals. Regulations should explicitly require data that would allow for the identification of known, presumed and suspected EDs used or to be used in any sector. The use of ED tests covering all ED modalities and endpoints, should be made compulsory in all application dossiers submitted by the industry. Increased means should be allocated for the control of substance application dossiers. More ambitious objectives should be set for the numbers of chemicals examined each year for their ED properties in national and EU agencies.

7. **Management of EDs across sectors (1):** EDs should be recognized as a class of hazard of equivalent concern to carcinogens, mutagens and reprotoxicants in all sectors and not only for pesticides and REACH chemicals, but also cosmetics, toys, food additives and food contact materials.
8. **Management of EDs across sectors (2):** In order to minimize ED exposure among EU citizens, the EU should move towards an identical management of EDs across all sectors for which ED use is very likely to entail population exposure. This includes in particular plant protection products, biocides, food contact materials and additives, consumer goods, cosmetics and toys. Established scientific facts show that (a) hormones act at extremely low doses; (b) EDs are expected to also act at low doses, and this is proven for the most studied EDs; (c) there are methodological limitations to the approaches typically used to identify so-called safe thresholds in regulatory toxicology and (d) the approaches commonly used to identify these safe thresholds generally do not consider cumulative effects of combined exposures. Hence, one option to protect human health and make the EU regulation more coherent across sectors would be to apply a logic similar to that already in use for pesticides, i.e. that substances identified as known or presumed EDs should not be authorized ("no exposure" logic) in products with general population exposure. For the cosmetic sector specifically, a logic similar to that applied for CMRs should be used for EDs, consisting in banning known, presumed and suspected EDs in cosmetics.
9. **Management of EDs in specific sectors (1) - Media-oriented regulations:** The oestrogenic, androgenic, thyroid, steroid (E, A, T, S) loads of food and drinking water should be evaluated and monitored, and the implementation of limit values for E, A, T, S activities should be considered, bearing in mind that such endocrine activity may be indicative of adverse effects.
10. **Management of EDs in specific sectors (2) - Occupational exposures:** Occupational exposure limits should be set for EDs.
11. **Surveillance of production, use and exposure to EDs:** Data on ED production, use of EDs across sectors should be gathered by the industry and relevant actors and made available at fine geographic and temporal scales. Monitoring known, presumed and suspected EDs (banned or still in use) in human populations (human biomonitoring) should be implemented in a harmonized way at the EU scale, including among pregnant women and children.
12. **Research priorities:** The current scientific knowledge, accumulated over the last 30 years, is sufficient to justify the above-mentioned recommendations. However, in order to identify new EDs, develop new tests and better quantify their population impacts, six areas of research are flagged: (i) Epigenetic effects of EDs; (ii) Concern beyond the current generation; (iii) ED effects on the microbiome, an essential component of physiological and immune responses (iv) Green (safe) chemistry; (v) Novel ED modalities (vi) Characterization of dose-response functions for ED effects in human.

Annex

ANNEX 1: DEFINITIONS

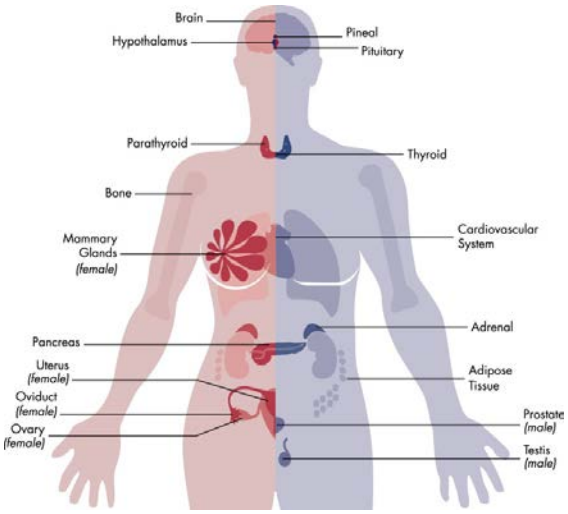
Adverse effect: A change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences

Adverse outcome: according to the OECD[77] an adverse outcome is a specialised type of key event that is of regulatory significance on the basis of correspondence to an established protection goal or equivalence to an apical endpoint in an accepted regulatory guideline toxicity test. Depending on whether the protection goal is for human health or ecological health the endpoints considered may differ.

Combined exposure: This concept refers to exposure to multiple chemicals by multiple routes, from one or multiple sources and/or use(s).

Endocrine disrupter (or disruptor): According to the WHO definition "an endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub)populations." [9]

Endocrine system: Multiple glands compose the endocrine system. All produce hormones that are secreted in low doses into the blood system from whence they act on other tissues see Section 1.3. Figure reproduced from [4] (No permission required).



Epigenetic: this term means literally "above the gene" and refers to changes in transcription that occur without modifying or mutating the DNA sequence, but changing when and where genes are expressed in different tissues and at different time points. Epigenetic effects most often implicated either DNA methylation or changes in chromatin structure (chromatin being the proteins surrounding the actual DNA sequence).

Mechanism of Action: According to the OECD [77], a mechanism of action for toxicity is the detailed molecular description of key events in the induction of cancer or other health endpoints. Mechanism of action represents a more detailed understanding and description of events that is meant by *mode of action* (see below).

Mode of Action: is defined by WHO as a "Biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data."

Risk: the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent [280].

Weight of Evidence (WoE): Weight of evidence assessment is defined … as a process in which evidence is integrated to determine the relative support for possible answers to a question. [The weight of evidence assessment comprises] three basic steps: (1) assembling the evidence into lines of evidence of similar type, (2) weighing the evidence, (3) integrating the evidence." (From EFSA guidance on weight of evidence, EFSA Journal, 2017, https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4971).

ANNEX 2: DISCUSSION OF PAST CONTROVERSIES REGARDING EDS REGULATION IN THE EU

2013 "ED criteria" and Dietrich et al. 2013 letter

In 2013, Daniel Dietrich and 18 colleagues (the large majority of whom did not declare their conflicts of interest, notably with the chemical industry) published a letter in a series of journals [262]. They had previously addressed the same letter to Dr. Glover, then Chief Scientific Advisor to Mr. Barroso (at that time EU Commission President) stating among other points that:

> "…we also think that the identification and regulation of such substances [EDs] should depend on a) the definition of adverse effects that are relevant to whole human or animal organisms and not to isolated test systems of unknown homeostatic significance, and b) on a characterization of real-life potency and therefore of thresholds of concern."

This commentary was countered by 30 clinical and basic endocrinologists (see for instance [281]), underlining the innumerable published studies that refuted the main arguments. Regarding specifically point a) it can be noted that the WHO definition of EDs and the current ED criteria applied in the EU for plant protection products and biocides do refer to adverse effects relevant to organisms and populations, which is in agreement with the commentary [262]

The second point regarding the *potency* concept was clearly refuted in several publications (see e.g. [94]); the point was debated and agreed by a group of scientists (several of which had signed the 2013 letter, including Dr. Dietrich) in a meeting convened by the German Institute for Risk Evaluation (BfR) in Berlin [98], who concluded in a consensus statement that:

> "This enabled the workshop participants to conclude that differences in opinion regarding the existence of thresholds and non-monotonic dose–response curves, although relevant to the risk characterization of EDs, are not a hindrance for defining scientific criteria for their identification." and that "…potency is not relevant for identification of a compound as an endocrine disruptor" [98].

A detailed account of the role of the chemical industry in inflecting and delaying the decision making process on EDs in 2013 was published by a non-governmental organisation [282].

2018 Parliament hearing at the PETI commission: statements from dr. Dietrich

In addition to the criticisms raised in Bond and Dietrich [242], in a hearing in the EU parliament in March 2018, Dr. Dietrich made several statements in a talk titled "Synthetic EDC [endocrine disrupting compounds] at the present human exposure ARE NO RISK for human health". Dr. Dietrich is a toxicologist working on cyanobacteria and mycotoxins, i.e. toxins of natural origin, but with very few original publications on the effects of man-made chemicals nor on endocrinology.

The recorded talk made several assertions. We discuss briefly the major ones.

1) Margin of exposure and naturally occurring EDs:

- Margin of exposures for environmental exposures are above 10,000 for most compounds.
- "Daidzein, genistein, BPA, DDE are GR [glucocorticoid receptor] agonists, but how potent are they?"
- "Daidzein and genistein levels were 10-100-fold lower than endogenous oestrogen levels. BPA [bisphenol A] levels were 100,000-fold lower than endogenous oestrogen levels"

These three comments do not take into account (i) the demonstrated cumulative effects of mixtures (see section 1.6) nor (ii) vulnerable periods of exposure (see section 1.7) nor non-linear responses and low dose effects (see section 1.3.3). The specific question of genistein and daidzein is dealt with in point 3 below.

Note also, with respect to the reference to *potency* in the second quote, that the Berlin consensus statement included this point stating (point 22) that:

> "We agree that a chemical's potency to induce an adverse effect is an important factor for consideration during the characterization of the hazards of endocrine disruptors. However, potency is not relevant for identification of a compound as an endocrine disruptor."

2) Pregnancy: "Endogenous hormone levels vary dramatically during pregnancy" (citing Teeguarden et al, March 2018).

This statement is obviously correct. Indeed, hundreds of million years of mammalian evolution have fine-tuned circulating and placental hormone levels in pregnancy to ensure appropriate homeostasis at different times and within appropriate compartments in pregnancy. (For a review of neuroendocrine mechanisms and pregnancy see [283]). Interference from EDs during this period, particularly the first trimester represents an exceedingly vulnerable period for exposure (see section 1.7). Notably, shifting the oestrogenic, androgenic or thyroid hormone levels during pregnancy away from the normal level, even by a very small amount, can have dramatic effects (see Figure 1).

3) Bisphenol F in mustard: "Intake of naturally occurring BPF [bisphenol F] from yellow mustard is similar if not greater than daily BPA [bisphenol A] exposure"

The fact that some people eating mustard may have higher exposure to bisphenol F than the average population exposure to bisphenol A bears no consequence at all regarding the innocuity of bisphenol A exposure (if this is what is meant by this statement). The two compounds are different, and there is no guarantee at all that bisphenol F exposure is safe; on the contrary, published evidence shows that it does exert ED effects [271].

It is well accepted that a small number of naturally occurring compounds can exert endocrine disrupting activity. Examples include genistein and daidzein found in soy products, that inhibit iodine uptake by the thyroid [284, 285] and displace thyroid hormone from one of its main transporter proteins [286]. Just like acknowledging the health impact of tobacco smoke and the need for decreased exposure does not diminish the impact of ambient air pollution on health, we cannot fathom why acknowledging bisphenol F exposure from natural sources would make the need for minimisation of bisphenol A exposure irrelevant.

4) BPA and the CLARITY Study: "The NTP [US-national toxicology program] Research Report on the CLARITY-BPA Core Study with rats February 2018 shows: "BPA produced minimal effects that were distinguishable from background in this study, particularly below 25,000 µg/kg body weight.day"

(note: distinguishable probably used for *un*distinguishable).

It is important to note that numerous publications arising from the Clarity-BPA study **do** show significant effects, notably on brain gene expression (see for instance [27], the recent review by Prins et al. [120] and references in section 2.2.1). Contrary to the statement above, there is evidence of effects of bisphenol A in the 1-10 µg/kg body weight.day range (reviewed e.g. in [120, 121]), that is, 2500 times below the dose quoted by Dr. Dietrich in his statement to the EU Parliament.

5) Criticism of the *alleged link between DDT exposure and obesity*, considered by Trasande et al. [287]:

Dr. Dietrich highlighted correlations between adult obesity and current DDT exposures (as opposed to prenatal exposures and childhood obesity), citing WHO figures on adult obesity from 2008, where Indonesia (which banned DDT use in 1994) and India ("which opposes a 2020 DDT ban") both show very low obesity levels at the country scale. One should note that such data at the region or country level correspond to so-called "ecological" studies, which provide a very low level of evidence. Such an approach does not in particular allow to control for potential confounders at the individual level (such as caloric intake and physical activity) as in epidemiological cohort studies, which generally provide a much stronger level of evidence. The ecological data provided by Dr. Dietrich do not even include a direct estimate of exposure to DDT, but a very indirect one related to the year when DDT was banned (which is a very imperfect indicator given the persistence of the compound and its main metabolite, DDE).

Furthermore, data from the US National Health and Nutrition Examination Study (NHANES) showed that "for a given amount of caloric intake, macronutrient intake or leisure time physical activity, the predicted BMI was up to 2.3 $kg.m^{-2}$ higher in 2006 than it was in 1988" [288]. Similarly, since the Trasande cost study in 2015 [287], further evidence for a link between prenatal DDT exposure and childhood obesity has been published [248].

6) Temporal trends in DDT in human breast milk and adipose tissue. *"The results support a continuing decrease in human body burdens of PCBs, DDE and HCB during the 1990s"*

That the body burden of certain persistent organic pollutants has decreased over time in many countries in the last decades is not debated. However, it is also not informative with respect to the impact of these compounds on obesity risk, given the prenatal exposure risk. Just like comparing countries (the so-called spatial "ecological approach" discussed above) generally provides very limited evidence regarding the effect of environmental factors, comparing temporal trends in exposure (e.g., to DDT) and health outcomes (e.g., obesity, that are on the rise in several countries) corresponds to a temporal ecological study, and is a very weak study design.

Similarly, the fact that UNEP figures show chemical production to have increased 300 fold since the 1970s [289] (when the bans on DDT and PCBs were enacted), argues for an overall increased chemical load on human and environmental exposure. In fact, innumerable human exposure studies show dozens or hundreds of chemicals in human fluids, including in amniotic fluids (see for instance [43] and references therein). This increased chemical load (including many confirmed and potential EDs) can exert additive or synergistic effects with those of banned persistent pollutants (such as DDT/DDE and PCBs).

7) "Current exposure levels of EDCs e.g. BPA and DDE are too low to have any effect on the foetus or the developing child."

This conclusion is not accompanied by any reference so that it is not easy to see what would justify it. The fact is that there are many solid demonstrations increased risk of disease following prenatal exposure to either bisphenol A or DDE (see sections 2.8.2 and 2.2.1). Furthermore, as argued immediately above, another major concern arises from potential mixture effects.

8) "Current exposures to isoflavones could have an added-on endocrine effect"

See response to point 3 above.

9) "Current exposures to known EDCs such as sugar will definitely have an adverse health effect."

This is undoubtedly the case, hence the need for better dietary advice and the need to argue for and even recommend lower sugar levels in certain foodstuffs (see also following point).

10) "Caloric intake will definitely have an adverse health effect"

As presented in section 2.8.2, data from the US National Health and Nutrition Examination Study (NHANES) showed that "for a given amount of caloric intake, macronutrient intake or leisure time physical activity, the predicted BMI was up to 2.3 $kg.m^{-2}$ higher in 2006 than it was in 1988" [288]. This finding argues for the presence of obesogenic EDs in our environment, as developed by Blumberg and colleagues [55].

11) "Our review of the Trasande et al human cost burden analyses uncovered substantial flaws in approach taken and conclusions drawn and therefore are highly speculative and should not be considered in weight of evidence approach."

The principle of weight of evidence approaches is precisely not to discard any study on the considered topic, but to include them all, with a weight depending on its quality.

See above (2.8.2) for a discussion of the Trasande et al. studies.

12) "EDCs follow a concentration response principle, with a threshold."

See response to point 1 above.

13) "With the exception of natural EDCs (sugar, isoflavones, BPF), prominent human diseases, e.g. prevalence of T2D [type-2 diabetes], are impossible to associate or causally relate or to synthetic EDC exposure based on the actual low concentrations found in exposed persons."

Numerous sections of this report refute this unsubstantiated claim (see 1.7, 1.8, chapter 2). Besides, there is no general scientific reason why only naturally-occurring EDs would have an effect and an impact, and not man-made EDs.

14) "Any regulation of EDCs should embrace in language and foreseen procedure:

- A. "causality" and not "plausibility" of the hazards determined in the in vivo, in vitro and in silico test systems used"
- B. Must consider potency of the compounds in question
- C. Must consider true human exposure (several age groups)
- D. Must consider the "more likely explanations" in a human disease, before an association of an EDC (or any other mechanism) with the specific disease is considered.

A: The ECHA/EFSA Guidance document for ED identification in plant protection products and biocides [255] emphasizes that "...the link between the adverse effect(s) and the endocrine mode of action shall be established based on biological plausibility". Causality is not a scientifically defined concept in environmental health, the current approach relies on statement about the overall level of evidence, established using weight of evidence methods, as enshrined in several parts of the EU regulation; this is what "plausibility" refers to. Further regulations could define several categories of EDs, distinguishing those with a high level of evidence (possibly corresponding to what is referred to here as "causal") from those for which evidence is lower (e.g., presumed and suspected EDs, which may have different regulatory implications).

B: As concluded in a meeting of scientists held in Berlin in 2016, "…potency is not relevant for identification of a compound as an endocrine disruptor." [98]. Note that potency is an ill-defined concept that pharmacologists recommend not to use [290] and that Dr. Dietrich is a co-author of the Berlin consensus article that was published following the meeting [98].

C: This statement can have several meanings. First, it can be noted that existing regulation of EDs already considers human exposure. For example, the 2009 plant protection products regulation states that plant protection products recognized as EDs shall not be authorized *unless human exposure is negligible*. In its recent communication on EDs (from November 2018), the European Commission called for a minimization of ED exposure for humans and the environment.

D. is a very simplistic view of environmental health sciences, that have over decades, developed various approaches to multifactorial health outcomes (see chapter 2, 2.1).

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CONFLICT OF INTERESTS STATEMENT AND ACKNOWLEDGEMENTS

Conflicts of interests' statement

The authors declare no financial conflict of interests.

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INDEX

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This study, commissioned by the PETI Committee of the European Parliament, presents the scientific knowledge regarding the health effects of endocrine disruptors, a class of hazards recognized in EU regulation since 1999. This report reviews the scientific evidence regarding the concept of endocrine disruption, the extent of exposure, associated health effects and costs. The existing relevant EU regulations are discussed and recommendations made to better protect human health.

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